

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 October 2003 (30.10.2003)

PCT

(10) International Publication Number
WO 03/089583 A2

(51) International Patent Classification⁷: C12N
(21) International Application Number: PCT/US03/11497
(22) International Filing Date: 15 April 2003 (15.04.2003)
(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data:
60/372,669 16 April 2002 (16.04.2002) US
60/374,823 24 April 2002 (24.04.2002) US
60/376,558 1 May 2002 (01.05.2002) US
60/381,366 20 May 2002 (20.05.2002) US
60/403,648 16 August 2002 (16.08.2002) US
60/411,882 20 September 2002 (20.09.2002) US
60/424,336 7 November 2002 (07.11.2002) US

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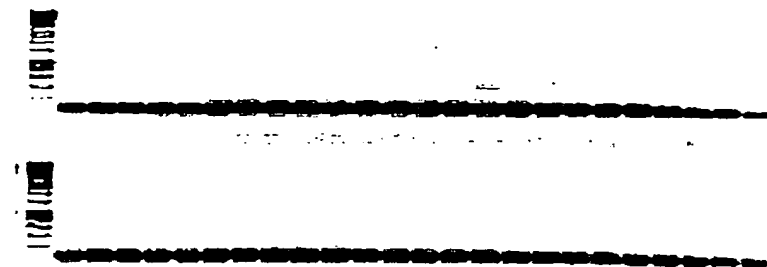
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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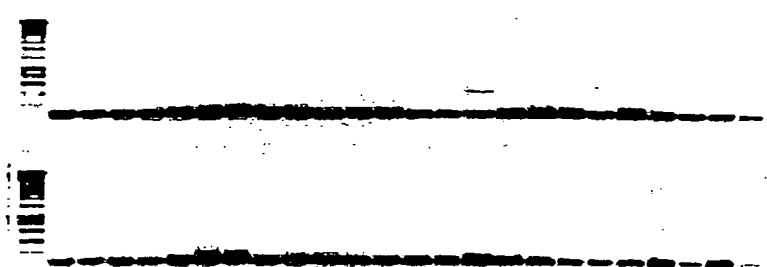
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(54) Title: TISSUE SPECIFIC GENES AND GENE CLUSTERS

XM_061784



XM_061785



(57) Abstract: The present invention relates to genes and genes clusters which are expressed in a tissue specific manner. For example, the invention relates to a group of genes encoding GPCR-like receptors that are involved in the function and activity of the immune system. These genes are organized into a discrete cluster at chromosomal location 1q22 (the "immune gene complex") and span about 700 kb of DNA. The region closest to the centromere comprises genes that are expressed predominantly in the thymus, while the distal region comprises genes which are expressed predominantly in the bone marrow and other hematopoietic cells. Another cluster of GPCR genes is located at chromosomal band 11q24. These genes are expressed predominantly in pancreatic tissue, establishing this region of chromosome 11 as a unique gene complex involved in

pancreatic function. A cluster of transmembrane and GPCR-type receptor genes is also located at chromosomal band 11q12.2. These genes are expressed predominantly in the spleen (hence, "spleen gene" cluster), as well as other tissues of the immune and reticuloendothelial system (RES), indicating that establishing this region of the chromosome is involved in spleen, lymphoid, and/or reticuloendothelial function. Finally, genes coding for membrane proteins have been identified which are expressed selectively in bone marrow, kidney, pancreas, and retina.

BEST AVAILABLE COPY

WO 03/089583 A2

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— of inventorship (Rule 4.17(iv)) for US only

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TISSUE SPECIFIC GENES AND GENE CLUSTERS

This application claims the benefit of U.S. Application Serial Nos. 60/372,669 April 16, 2002, 60/374,823 filed April 24, 2002, 60/376,558 filed May 1, 2002, 60/381,366 filed May 20, 2002, 60/403,648 filed August 16, 2002, 60/411,882 filed September 20, 2002, and 60/424,336 filed November 7, 2002, which are hereby incorporated by reference in their entirety.

DESCRIPTION OF THE DRAWINGS

Figs. 1 and 2 show a physical map of the immune system gene complex. Sequence-tagged site ("STS") markers are used to characterize the chromosomal regions. An STS is defined by two short synthetic sequences (typically 20 to 25 bases each) that have been designed from a region of sequence that appears as a single-copy in the human genome (the reference numbers, and the sequences which they represent, are hereby incorporated by reference in their entirety). These sequences can be used as primers in a polymerase chain reaction (PCR) assay to determine whether the site is present or absent from a DNA sample.

Fig. 3 shows the expression pattern of transmembrane proteins homologous to the olfactory G-protein-coupled receptor ("GPCR") family in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 5 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Fig. 4 shows the expression pattern of two olfactory G-protein-coupled receptor ("GPCR") family members in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 6 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Figs. 5 (a and b) and 6 show the expression pattern in human tissues of genes selectively expressed in kidney tissue. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 11 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Fig. 7 (a-b) show organization of pancreatic gene complex on chromosome 11q24.

Fig. 8 is a schematic drawing of five of the pancreatic olfactory G-protein-coupled receptor ("GPCR") family members located in the gene complex showing regions of overlap. The numbering underneath the lines indicates amino acid position.

Fig. 9 (a and b) show the expression pattern of TMD0986, XM_061780 (TMD0987),
 5 XM_061781 (TMD0353), XM_061784 (TMD0989), and XM_061785 (TMD058) in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 12 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Fig. 10 shows the expression pattern of TMD1030 (XM_166853), TMD1029
 10 (XM_166854), TMD1028 (XM_166855), and TMD0621 (XM_166205) in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 17 indicates the SEQ ID NO for each primer ("F-oligo" is the forward primer and "R-oligo" is the reverse primer).

Fig. 11 shows the organization of the spleen gene complex on chromosome 11q12.2.

15 Fig. 12 (a-c) shows the expression of the pancreas genes in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 23 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Expression patterns were analyzed as described below. A twenty-four tissue panel
 20 was used (lanes from left to right): 1, adrenal gland; 2, bone marrow; 3, brain; 4, colon; 5, heart; 6, intestine; 7, pancreas; 8, liver; 9, lung; 10, lymph node; 11, lymphocytes; 12, mammary gland; 13, muscle; 14, ovary; 15, pancreas; 16, pituitary; 17, prostate; 18, skin; 19, spleen; 20, stomach; 21, testis; 22, thymus; 23, thyroid; 24, uterus. The lane at the far left of each panel contains molecular weight standards. Polyadenylated mRNA was isolated from
 25 tissue samples, and used as a template for first-strand cDNA synthesis. The resulting cDNA samples were normalized using beta-actin as a standard. For the normalization procedure, PCR was performed on aliquots of the first-strand cDNA using beta-actin specific primers. The PCR products were visualized on an ethidium bromide stained agarose gel to estimate the quantity of beta-actin cDNA present in each sample. Based on these estimates, each
 30 sample was diluted with buffer until each contained the same quantity of beta-actin cDNA per unit volume. PCR was carried out using the primers described above, and reaction

products were loaded on to an agarose (e.g., 1.5-2%) gel and separated electrophoretically.

DESCRIPTION OF THE INVENTION

The present invention relates to tissue-selective genes and tissue-selective gene
5 clusters. The polynucleotides and polypeptides are useful in variety of ways, including, but
not limited to, as molecular markers, as drug targets, and for detecting, diagnosing, staging,
monitoring, prognosticating, preventing or treating, determining predisposition to, etc.,
diseases and conditions, associated with genes of the present invention. The identification of
specific genes, and groups of genes, expressed in pathways physiologically relevant to
10 particular tissues, permits the definition of functional and disease pathways, and the
delineation of targets in these pathways which are useful in diagnostic, therapeutic, and
clinical applications. The present invention also relates to methods of using the
polynucleotides and related products (proteins, antibodies, etc.) in business and computer-
related methods, e.g., advertising, displaying, offering, selling, etc., such products for sale,
15 commercial use, licensing, etc.

Immune Gene Complex

The present invention relates to a group of genes involved in the function and activity
of the immune system. These genes are organized into a discrete cluster at chromosomal
20 location 1q22 (the "immune gene complex") and span hundreds of kb of DNA, e.g., about
700 kb of DNA. See, Figs. 1 and 2. The region closest to the centromere comprises genes
that are expressed predominantly in the thymus, while the distal region comprises genes
which are expressed predominantly in the bone marrow and other hematopoietic cells.

The present invention relates to a composition consisting essentially of the 1q22
25 immune gene complex, comprising TMD0024 (XM_060945), TMD1779 (XM_060946),
TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781
(XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890
(XM_060959) genes, or a fragment thereof comprising at least two said genes. As discussed
in more detail, the composition can comprise or consist essentially of the chromosome region
30 between STS markers that define the genomic DNA, e.g., between SHGC-81033 and SHGC-
145403, or a fragment thereof comprising at least two said genes.

The CD1 family, a cluster of genes previously identified as coding for proteins involved in antigen presentation (Sugita and Brenner, *Seminars in Immunology*, 12:511-516, 2000), are located at the proximal boundary of the immune gene complex. The expression of CD1a, b, and c genes are restricted to professional antigen-presenting cells, including dendritic cells and some B-cell subsets (Sugita and Brenner, *ibid*). CD1d is present on other cell types, in addition to hematopoietic cells, such as intestinal cells (Sugita and Brenner, *ibid*).

Adjacent to the CD1 family, is a cluster of genes coding for transmembrane proteins homologous to the olfactory G-protein-coupled receptor ("GPCR") family. These genes include XM_060945 (TMD0024), XM_060346 (TMD1779), XM_060947 (TMD0884), and XM_060948 (TMD0025), and are expressed predominantly in thymus tissues (e.g., thymocytes). XM_089421 (TMD1781) is also expressed in thymus, but it is present in much higher amounts in lymphocytes ("PBL"). This chromosomal region can be defined by STS markers, e.g., between SHGC-81033 and D1S3249, G15944, GDB:191077, GDB:196442, RH68459, RH102597, RH69635, or RH65132, or fragments thereof, such as fragments which comprise two or more genes.

The gene for human erythroid alpha spectrin (SPTA1) is distal to the GPCR thymus-restricted family. It is expressed in bone marrow cells, and is localized to the red cell membrane (Wilmotte et al., *Blood*, 90(10):4188-96, 1997). Next to it, is another cluster of genes coding for proteins that resemble the olfactory GPCR family. These include XM_060956 (TMD0304), XM_060957 (TMD0888), and XM_060959 (TMD089), and are expressed predominantly in the bone marrow, although other sites of expression are observed as well. See, e.g., Table 1. This chromosomal region can be defined by STS markers, e.g., between GDB:181583 or RH118729, and D1S2577 or SHGC-145403.

The gene for myeloid cell nuclear differentiation antigen ("MNDA") is next. MNDA is also expressed in bone marrow cells, particularly in normal and neoplastic myelomonocytic cells and a subset of normal and neoplastic B lymphocytes (Miranda et al., *Hum. Pathol.*, 30(9):1040-9, 1999).

The phrase "immune system" indicates any processes and cells which are involved in generating and carrying out an immune response. Immune system cells includes, but are not limited to, e.g., stem cells, pluripotent stem cell, myeloid progenitor, lymphoid progenitor,

lymphocytes, B-lymphocytes, T-lymphocytes (e.g., naive, effector, memory, cytotoxic, etc.), thymocytes, natural killer, erythroid, megakaryocyte, basophil, eosinophil, granulocyte-monocyte, accessory cells (e.g., cells that participate in initiating lymphocyte responses to antigens), antigen-presenting cells ("APC"), mononuclear phagocytes, dendritic cells,
5 macrophages, alveolar macrophages, etc., and any precursors, progenitors, or mature stages thereof.

Table 1 is a summary of the genes and their expression patterns in accordance with the present invention. The genes and the polypeptides they encode can be used as diagnostic, prognostic, therapeutic, and research tools for any conditions, diseases, disorders, or
10 applications associated with the tissues and cells in which they are expressed.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule
15 comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

20 In view of their selectivity and display on the cell surface, the olfactory GPCR family members of the present invention are a useful target for histological, diagnostic, and therapeutic applications relating to the cells in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging,
25 therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies to identify bone marrow and thymus tissue, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to
30 target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the

polypeptide which are exposed extracellularly as indicated in Table 2. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo (e.g., bone marrow cells or peripheral blood lymphocytes can be treated ex vivo and then returned to the body).

5 The expression patterns of the selectively expressed polynucleotides disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by a tissue. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of expressed sequences disclosed herein provides an example of such a tissue expression profile. It can be used as a point of reference
10 to compare and characterize samples. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue, to determine the origin of metastatic cells, to assess the physiological status of a tissue, to determine the effect of a particular treatment regime on a tissue, to evaluate the toxicity of a compound on a tissue of interest, etc.

 For example, the tissue-selective polynucleotides disclosed herein represent the
15 configuration of genes expressed by a normal tissue. To determine the effect of a toxin on a tissue, a sample of tissue can be obtained prior to toxin exposure ("control") and then at one or more time points after toxin exposure ("experimental"). An array of tissue-selective probes can be used to assess the expression patterns for both the control and experimental samples. As discussed in more detail below, any suitable method can be used. For instance,
20 a DNA microarray can be prepared having a set of tissue-selective genes arranged on to a small surface area in fixed and addressable positions. RNA isolated from samples can be labeled using reverse transcriptase and radioactive nucleotides, hybridized to the array, and then expression levels determined using a detection system. Several kinds of information can be extracted: presence or absence of expression, and the corresponding expression levels.
25 The normal tissue would be expected to express substantially all the genes represented by the tissue-selective probes. The various experimental conditions can be compared to it to determine whether a gene is expressed, and how its levels match up to the normal control.

 While the expression profile of the complete gene set represented by the sequences disclosed here may be most informative, a fingerprint containing expression information
30 from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify

-7-

the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, because of heterogeneity of the population, as well differences in the particular physiological state of the tissue, a tissue's "normal" expression profile is expected to differ between samples, albeit in ways that do not change the overall expression pattern. As a result of these individual differences, each gene although expressed selectively in spleen, may not on its own 100% of the time be adequately enough expressed to distinguish said tissue. Thus, the genes can be used in any of the methods and processes mentioned above and below as a group, or one at a time.

Binding partners can also be used as to specifically deliver therapeutic agents to a tissue of interest. For example, a gene to be delivered to a tissue can be conjugated to a binding partner (directly or through a polymer, etc.), in liposomes comprising cell surface, and then administered as appropriate to the subject who is to be treated. Additionally, cytotoxic, cytostatic, and other therapeutic agents can be delivered specifically to the tissue to treat and/or prevent any of the conditions associated with the tissue of interest.

The present invention relates to methods of detecting immune system cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene selected from Table 1, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 3, 4, 8, 9, 14, 15, 22, 23, 27, 28, 35, 36, 42, 43, 49, 50, 57, and 58 (see, Table 5), and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting an immune system cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by gene selected from Table 1, or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be

accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 2.

As indicated above, binding partners can be used to deliver agents specifically to the immune system, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to an immune cell can comprise, e.g., contacting an immune cell with an agent coupled to binding partner specific for a gene selected from Table 1 (i.e., TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959)), whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the immune system can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

The maturation of the immune system can also be modulated in accordance with the

present invention, e.g., by methods of modulating the maturation of an immune system cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 1, or a mammalian homolog thereof, whereby the maturation of an immune cell is modulated. Modulation as used throughout
5 includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

The phrase "immune system cell maturation" includes indirect or direct effects on immune system cell maturation, i.e., where modulating the gene directly effects the maturational process by modulating a gene in a immune system cell, or less directly, e.g.,
10 where the gene is expressed in a cell-type that delivers a maturational signal to the immune system cell. Immune system maturation includes B-cell maturation, T-cell maturation, such as positive selection, negative selection, apoptosis, recombination, expression of T-cell receptor genes, CD4 and CD8 receptors, antigen recognition, MHC recognition, tolerization, RAG expression, differentiation, TCR expression, antigen expression, etc. See also below
15 and, e.g., Abbas et al., *Cellular and Molecular Immunology*, 4th Edition, W.B. Saunders Company, 2000, e.g., Pages 149-160. Process include reception of a signal, such as cytokinin or other GPCR ligand. Any suitable agent can be used, e.g., agents that block the maturation, such as an antibody to a GPCR of Table 1, or other GPCR antagonist.

The interactions between lymphoid and non-lymphoid immune system cells can also
20 be modulated comprising, e.g., contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 1, or a mammalian homolog thereof, whereby the interaction is modulated. Lymphoid cells, includes, e.g., lymphocytes (T- and B-), natural killer cells, and other progeny of a lymphoid progenitor cell. Non-lymphoid cells include accessory cells, such as antigen presenting cells, macrophages,
25 mononuclear phagocytes dendritic cells, non-lymphoid thymocytes, and other cell types which do not normally arise from lymphoid progenitors. Interactions that can be modulated included, e.g., antigen presentation, positive selection, negative selection, progenitor cell differentiation, antigen expression, tolerization, TCR expression, apoptosis. See, also above and below, for other immune system processes.

30 Promoter sequences obtained from GPCR genes of the present invention can be utilized to selectively express heterologous genes in immune system cells. Methods of

expressing a heterologous polynucleotide in immune system cells can comprise, e.g.,
expressing a nucleic acid construct in immune system cells, said construct comprising a
promoter sequence operably linked to said heterologous polynucleotide, wherein said
promoter sequence is selected from Table 5. In addition to the cell lines mentioned below,
5 the construct can be expressed in primary cells, such as thymocytes, bone marrow cells, stem
cells, lymphoid progenitor cells, myeloid progenitor cells, monocytes, antigen presenting
cells, macrophages, and cell lines derived therefrom, cell lines such as JHK3 (CRL-10991),
KG-1 (CCL-246), KG-1a (CCL-246.1), U-937 (CRL-1593.2), VA-ES-BJ (CRL-2138), TUR
(CRL-2367), ELI (CRL-9854), 28SC (CRL-9855), KMA (CRL-9856), THP-1 (TIB-2002),
10 WEHI-231 (CRL-1679), M-NFS-60 (CRL-1838), MH-S (CRL-2019), SR-4987 (CRL-
2028), NCTC 3749 (CCL-461), AMJ2-C8 (CRL 2455), AMJ2-C11 (CRL2456), PMJ2-PC
(CRL-2457), EOC2 (CRL-2467), as well as any primary and established immune system cell
lines.

15 Thymus

The thymus is the site of T-cell lymphocyte maturation. Immature lymphocytes
migrate into the thymus from the bone marrow and other organs in which they are generated.

The selection process that shape the antigen repertoire of T-cells takes place in the thymus
organ. Both positive and negative selection processes take place. For a review, see, e.g.,

20 Abbas et al., Cellular and Molecular Immunology, 4th Edition, W.B. Saunders Company,
2000, e.g., Pages 126-130 and 149-160.

There are various diseases and disorders related to thymus tissue, including, but not
limited to, thymic carcinoma, thymoma, Omenn syndrome, autoimmune diseases, allergy,
Graves disease, Myasthenia gravis, thymic hyperplasia, DiGeorge syndrome, Good
25 syndrome, promoting immune system regeneration after bone marrow transplantation,
immuno-responsiveness, etc. The thymic selective genes and polypeptides encoded thereby
can be used to treat or diagnose any thymic condition. For instance, chemotherapeutic and
cytotoxic agents can be conjugated to thymic selective antibodies and used to ablate a
thymoma or carcinoma. They can be used alone or in combination with other treatments.

30 See, e.g., Graeber and Tamin, Semin. Thorac. Cardiovasc. Surg., 12:268-277, 2000; Loehrer,
Ann. Med., 31 Suppl. 2:73-79, 1999.

Bone marrow

All circulating blood cells in the adult, including all immature lymphocytes, are produced in the bone marrow. In addition, the bone marrow is also the site of B-cell maturation. The marrow consists of a spongelike reticular framework located between long trabeculae. It is filled with fat cells, stromal cells, and precursor hematopoietic cells. The precursors mature and exit through the vascular sinuses

All the blood cells are believed to arise from a common stem cell. Lineages that develop from this common stem cell include, e.g., myeloid and lymphoid progenitor cells. The myeloid progenitor develops into, erythrocytes (erythroid), platelets (megakaryocytic), basophils, eosinophils, granulocytes, neutrophils, and monocytes. The lymphoid progenitor is the precursor to B-lymphocytes, T-lymphocytes, and natural killer cells.

There are various diseases and disorders related to bone marrow, including, not limited to, e.g., red cell diseases, aplastic anemia (e.g., where there is a defect in the myeloid stem cell), pure red cell aplasia, white cell diseases, leukopenia, neutropenia, reactive (inflammatory) proliferation of white cells and nodes such as leukocytosis and lymphadenitis, neoplastic proliferation of white cells, malignant lymphoma, Non-Hodgkin's Lymphomas, Hodgkins disease, acute leukemias (e.g., acute lymphoblastic leukemia, acute myeloblastic leukemia, myelodysplastic syndrome), chronic myeloid leukemia, chronic leukemia, hairy cell leukemia, myeloproliferative disorders, plasma cell disorders, multiple myeloma, histiocytoses, etc.

Immune System Selective Genes

The present invention relates to genes involved in the function and activity of the immune system. XM_062147 (TMD0088) and XM_061676 (TMD0045) code for seven membrane spanning polypeptides which are homologous to members of the olfactory G-protein-coupled receptor ("GPCR") family. XM_062147 is expressed predominantly in bone marrow tissue, with no detectable expression in other tissues. XM_061676 is also expressed predominantly in bone marrow tissue, but it is detected in peripheral blood lymphocytes, as well. As discussed in more detail below, XM_062147 (TMD0088), XM_061676 (TMD0045), and the polypeptides they encode, can be used as diagnostic, prognostic, therapeutic, and research tools for any conditions, diseases, disorders, or applications

associated with the immune system and the cells in which they are expressed.

In view of their selectivity and display on the cell surface, the GPCR family members of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., B-cells and B-cell progenitors) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies to identify bone marrow, lymphocytes, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 2. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo (e.g., bone marrow cells or peripheral blood lymphocytes can be treated ex vivo and then returned to the body). Ex vivo methods can be used to eliminate cancerous cells from the bone marrow, to modulate bone marrow cells, to prime bone marrow cells for an immune response, to expand a particular class of cells expressing XM_062147 (TMD0088) or XM_061676 (TMD0045), to transfer genes into said cells (e.g., Banerjee and Bertino, *Lancet Oncol.*, 3:154-158, 2002), etc.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The phrase "immune system" indicates any processes and cells which are involved in

generating and carrying out an immune response. Immune system cells includes, but are not limited to, e.g., stem cells, pluripotent stem cell, myeloid progenitor, lymphoid progenitor, lymphocytes, B-lymphocytes, T-lymphocytes (e.g., naive, effector, memory, cytotoxic, etc.), thymocytes, natural killer, erythroid, megakaryocyte, basophil, eosinophil, granulocyte-
5 monocyte, accessory cells (e.g., cells that participate in initiating lymphocyte responses to antigens), antigen-presenting cells ("APC"), mononuclear phagocytes, dendritic cells, macrophages, etc., and any precursors, progenitors, or mature stages thereof.

XM_062147 contains seven transmembrane segments. It is located on chromosomal band 11q12 within proximity to the locus for an inherited form of atopic hypersensitivity
10 (OMIM 147050, e.g., associated with asthma, hay fever, and eczema). It has been suggested that the condition is a result of defect in the regulation of immunoglobulin E. XM_061676 also is seven membrane spanning polypeptide. The chromosomal locus, 11p15, to which it maps is rich in genes associated with immune disorders, including Fanconi anemia, nucleoporin, myeloid leukemia, and T-cell lymphoblastic leukemia. Arthrogryposis
15 multiplex congenita (distal type IIB) also maps closely to this chromosomal location.

The present invention relates to methods of detecting immune system cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene selected from Table 6, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said
20 gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 67, 68, 76, and 77 (see, Table 6), and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,
25 monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting an immune system cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by gene selected from Table 6, or a
30 mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be

accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 7.

As indicated above, binding partners can be used to deliver agents specifically to the immune system, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to an immune cell can comprise, e.g., contacting an immune cell with an agent coupled to binding partner specific for a gene selected from Table 6, whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the immune system can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

The maturation of the immune system can also be modulated in accordance with the present invention, e.g., by methods of modulating the maturation of an immune system cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 6, or a mammalian homolog thereof,

whereby the maturation of an immune cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

The phrase "immune system cell maturation" includes indirect or direct effects on
5 immune system cell maturation, i.e., where modulating the gene directly effects the
maturation process by modulating a gene in a immune system cell, or less directly, e.g.,
where the gene is expressed in a cell-type that delivers a maturational signal to the immune
system cell. Immune system maturation includes B-cell maturation, T-cell maturation, such
as positive selection, negative selection, apoptosis, recombination, expression of T-cell
10 receptor genes, CD4 and CD8 receptors, antigen recognition, MHC recognition, tolerization,
RAG expression, differentiation, TCR expression, antigen expression, etc. See also below
and, e.g., Abbas et al., *Cellular and Molecular Immunology*, 4th Edition, W.B. Saunders
Company, 2000, e.g., Pages 149-160. Processes include reception of a signal, such as
cytokinin or other GPCR ligand. Any suitable agent can be used, e.g., agents that block the
15 maturation, such as an antibody to a GPCR of Table 6, or other GPCR antagonist.

The interactions between lymphoid and non-lymphoid immune system cells can also
be modulated comprising, e.g., contacting said cells with an agent effective to modulate a
gene, or polypeptide encoded thereby, selected from Table 6, or a mammalian homolog
thereof, whereby the interaction is modulated. Lymphoid cells, includes, e.g., lymphocytes
20 (T- and B-), natural killer cells, and other progeny of a lymphoid progenitor cell. Non-
lymphoid cells include accessory cells, such as antigen presenting cells, macrophages,
mononuclear phagocytes dendritic cells, non-lymphoid thymocytes, and other cell types
which do not normally arise from lymphoid progenitors. Interactions that can be modulated
included, e.g., antigen presentation, positive selection, negative selection, progenitor cell
25 differentiation, antigen expression, tolerization, TCR expression, apoptosis. See, also above
and below, for other immune system processes.

Promoter sequences obtained from GPCR genes of the present invention can be
utilized to selectively express heterologous genes in immune system cells. Methods of
expressing a heterologous polynucleotide in immune system cells can comprise, e.g.,
30 expressing a nucleic acid construct in immune system cells, said construct comprising a
promoter sequence operably linked to said heterologous polynucleotide, wherein said

promoter sequence is selected from Table 6. In addition to the cell lines mentioned below, the construct can be expressed in primary cells, such as thymocytes, bone marrow cells, stem cells, lymphoid progenitor cells, myeloid progenitor cells, monocytes, B-cells, antigen presenting cells, macrophages, and cell lines derived therefrom.

5

Kidney Selective Genes

The present invention relates to genes and polypeptides which are selectively expressed in kidney tissues: TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736),
10 TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108). These genes and polypeptides are expressed predominantly in kidney tissues, making them, and the polypeptides they encode, useful as selective markers for kidney tissue and function, as well as diagnostic, prognostic, therapeutic, and research tools for any conditions, diseases,
15 disorders, or applications associated with the kidney and the cells in which they are expressed. TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108) includes both
20 human and mammalian homologs of it. SEQ ID NOS 78-103 represent particular alleles, but the present invention relates to other alleles, including naturally-occurring polymorphisms (i.e., a polymorphism in the nucleotide sequence which is identified in populations of mammals) and homologs thereof. More information on these genes is summarized in Tables 8-11.

25 In view of their selectivity and display on the cell surface, the polypeptides and polynucleotides of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., juxtaglomerular cells which secrete renin, peritubular cells, endothelial cells, e.g., of the cortex and outer medulla, mesangial cells which secrete inflammatory mediators including NO and products of cyclooxygenase,
30 visceral epithelial cells, parietal epithelial cells, podocytes, early proximal tubule cells which secrete, e.g., angiotensin converting enzyme and neutral endopeptidase, late distal tubule

cells that produce, e.g., prolyl endopeptidase, serine endopeptidase, carboxypeptidase, and neutral endopeptidase, renomedullary interstitial cells, etc) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies, to identify kidney, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 9. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The present invention relates to methods of detecting kidney cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below,

such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 104, 105, 107, 108, 111, 112, 115, 116, 119, 120, 122, 123, 126, 127, 131, 132, 135, 136, 138, 139, 142, 143, 145, 146, 149, 150, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,
5 monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a kidney cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by TMD0049 (XM_057351), TMD0190
10 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding
15 assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 9.

As indicated above, binding partners can be used to deliver agents specifically to the kidney, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an
20 agent to a kidney cell can comprise, e.g., contacting a kidney cell with an agent coupled to binding partner specific for TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), whereby said
25 agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the kidney can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried
30 specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target),

present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108) can be targeted, including, e.g., juxtaglomerular, peritubular, endothelial, mesangial, visceral epithelial, parietal epithelial, podocytes, early proximal tubule, late distal tubule, renomedullary interstitial, etc.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

A kidney cell (see above for examples of kidney cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a kidney cell, comprising, e.g., contacting said cell with an agent effective to modulate TMD0049

(XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), or the biological activity of a polypeptide encoded thereby, or a mammalian homolog thereof, whereby said kidney cell is modulated.

Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

An activity or function of the kidney cell can be modulated, including, e.g., glomerular filtration rate, filtration pressure, renal autoregulation (including via myogenic mechanism and tubuloglomerular feedback mechanism), tubular reabsorption, tubular secretion, and renal clearance. In addition, the transcription, translation, synthesis, degradation, expression, etc., of any secretory or polypeptide produced by a kidney cell can be modulated, including, but not limited to, renin-angiotensin activity, production and secretion of prostaglandins, nitric oxide, kallikrein, adenosine, endothelin, erythropoietin, and other hormones, enzymes, and other secretory and intracellular factors. The response of a kidney cell to stimuli can also be modulated, including, but not limited to, ligands to

5 TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), oxygen levels, blood pressure, etc.

The present invention also relates to polypeptide detection methods for assessing kidney function, e.g., methods of assessing kidney function, comprising, detecting a polypeptide coded for by TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), fragments thereof, polymorphisms thereof, in a body fluid, whereby the level of said polypeptide in said fluid is a measure of kidney function. Kidney function tests are usually performed to determine whether the kidney is functioning normally as a way of diagnosing kidney disease.

Various tests are commonly used, including, e.g., BUN (blood urea nitrogen), serum creatinine, estimated GFR, ability to concentrate urine, BUN/creatinine ratio, urine sodium and other electrolytes, urine NAG (N-acetyl-beta-glucosaminidase, adenosine deaminase, urinary alkaline phosphatase, serum and urine beta-2-microglobulin, serum uric acid, isotope scans, Doppler sonogram, positron emission tomography, specific gravity of urine, microalbumin, total protein, etc. Detection of TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148

(XM_087108) provides an additional assessment tool, especially in diseases such as chronic renal failure, urinary tract infections, kidney stones, nephrotic syndrome, nephritic syndrome, kidney disease due to diabetes or high blood pressure, etc., As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired kidney function.

- 5 Values can be determined routinely, as they are for other kidney function markers, such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc.

- Promoter sequences obtained from genes of the present invention can be utilized to selectively express heterologous genes in kidney cells. Methods of expressing a heterologous polynucleotide in kidney cells can comprise, e.g., expressing a nucleic acid construct in kidney cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NOS 106, 109, 110, 113, 114, 117, 118, 121, 124, 125, 128-130, 133, 134, 137, 140, 141, 144, 147, 148, and 151. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.
- 10
15

Kidney

- The kidney maintains the constancy of fluids in an organism's internal environment, and is therefore of great importance in maintaining health and vitality. Each day, the kidney filters the blood, removing and concentrating toxins, metabolic wastes, and excess ions, allowing them to be excreted by the body in the form of urine. The excretory function of the kidney is performed by over one million blood units called nephrons, each a miniature blood filtering and processing unit. A nephron consists of a glomerulus, a tuft of capillaries, and a renal tubule. In addition to their excretory function, kidneys produce a number of different hormones, enzymes, and other secreted molecules, including the enzyme renin and the hormone erythropoietin. The kidney also is responsible for metabolizing vitamin D into its active form, calcitriol. For a full description of the kidney's function and structure, see, e.g., *Human Anatomy and Physiology*, Marieb, E.N., 3rd Edition, Benjamin/Cummings Publishing Company, Inc., 1995, pp 896-923.
- 20
25

- The glomerulus is a high pressure capillary bed which filters out most substances smaller than large plasma proteins across the fenestrated glomerular epithelium, the
- 30

intervening basement membrane, and the podocyte-containing visceral membrane of the glomerulus capsule. The external layer of the glomerulus is called the parietal layer, consisting predominally of a squamous epithelium. This layer is structural. Underneath it, is the visceral layer which consists of the modified branching epithelial cells called podocytes.

- 5 These sit on top of the fenestrated glomerular endothelium. The glomerulus is connected to the renal tubule, a highly differentiated and long tube, having three major elements: the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule. Different regions of the tubule have different functions in absorption and secretion.

- Renal cells produce a variety of different hormones and chemicals, including,
 10 prostaglandins, nitric oxide, kallikrein family, adenosine, endothelin family, renin, erythropoietin, aldosterone, antidiuretic hormone (vasopressin), natriuretic hormones, etc. Renin is involved in modulating blood pressure. It cleaves angiotensinogen, a plasma peptide, splitting off a fragment containing 10 amino acids called angiotensin I. Angiotensin I is cleaved by a peptidase secreted by blood vessels called angiotensin converting enzyme
 15 (ACE), producing angiotensin II, which contains 8 amino acids. Angiotensin II has many direct effects on blood pressure. Erythropoietin stimulates red blood cell production in the bone marrow.

- TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719
 20 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108) can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the kidney. These include, but are not limited to, diseases that affect the four basic morphologic components, glomeruli, tubules, interstitium, and blood vessels. Diseases
 25 include, e.g., acute nephritic syndrome, nephritic syndrome, renal failure, urinary tract infections, renal stones, cystic diseases of the kidney, e.g., cystic renal dysplasia, polycystic disease (autosomal dominant and recessive types), medullary cystic disease, acquired cystic disease, renal cysts, parenchymal cysts, perihilar renal cysts (pyelocalyceal cysts, hilar lymphangitic cysts), glomerular diseases, diseases of tubules, tubulointerstitial diseases,
 30 tumors of the kidney, such as benign tumors (cortical adenoma, renal fibroma, renomedullary interstitial cell tumor), malignant tumors (renal cell carcinoma, hypernephroma,

adenocarcinoma of kidney, Wilms' tumor, nephroblastoma, urothelial carcinoma), renal coloboma, nephroblastoma, clear cell sarcoma of kidney (CCSK), rhabdoid tumor of kidney (RTK), von Hippel-Lindau disease, oncocytoïd renal cell carcinoma (RCC), renal leiomyoblastoma, etc. TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108) can also be used for staging and classifying conditions and diseases of the present invention, alone, or in combination with conventional staging and classification schemes.

10

Pancreatic Gene Complex

The present invention relates to a cluster of olfactory GPCR (G-protein coupled) receptor genes located at chromosomal band 11q24. These genes are expressed predominantly in pancreatic tissue, establishing this region of chromosome 11 as a unique gene complex involved in pancreatic function. See, Table 12. Because of their exquisite selectivity for pancreatic tissues, the pancreatic gene complex ("PGC"), and the genes which comprise it, are useful to assess pancreas tissue and function for diagnostic, prognostic, therapeutic, and research purposes.

The spatial organization of the pancreatic gene complex ("PGC") is illustrated in Fig. 7. It spans several hundred kilobases of chromosome 11, e.g., from about LOC160205 to LOC119954, from about LOC119944-LOC119954, and any part thereof. Within this region, is a cluster of genes coding for polypeptides which share sequence identity with the olfactory GPCR family. These include, but are not limited to, TMD0986, XM_061780 (TMD0987), XM_061781 (TMD0353), XM_061784 (TMD0989), XM_061785 (TMD058). Fig. 8 illustrates the relationship between the lengths of the different coding sequences. As shown in the figure, XM_061784 is shorter at its C-terminus than the other family members.

As members of the GPCR family, the PGC genes all share a degree of amino acid sequence identity and similarity. See, Table 14 for values (% sequence identity is the first place; % sequence similarity is in parenthesis in the second place; calculations were performed using the publicly-available BLASTP pair-wise alignment program). TMD0986, XM_061780, XM_061781, and XM_061785 each share about 40% sequence identity.

BLAST searching of publicly available sequences indicates that these polypeptides share less amino acid sequence identity with each other than they do with other olfactory GPCR homologs located elsewhere in the genome. Significantly higher amino acid sequence identity – 81% – is observed between the adjacent genes XM_061784 and XM_061785.

- 5 These genes appear to be part of a sub-cluster within PGC that share high polypeptide similarity between them.

The phrase “a gene of Table 12” which is used throughout the description include the specific sequences for the listed XM numbers as well as other human alleles, and mammalian homologs, such as murine homologs. For example, Table 14 lists several of the mouse
10 homologs that are included in the present invention. While SEQ ID NOS. 152, 153, 162, 163, 167, 168, 171, 172, 175, and 176 may represent particular alleles, the present invention relates to other alleles, as well, including naturally-occurring polymorphisms (i.e., a polymorphism in a nucleotide sequence which is identified in populations of mammals).

TMD0986 (SEQ ID NO 152 and 153) is a full-length sequence of the previously
15 identified XM_061779. It contains an additional 117 amino acids not present in XM_061779. The present invention relates to nucleic acids comprising or consisting essentially of this sequence in its entirety (e.g., amino acids 1-314), comprising or consisting essentially of nucleic acids coding for amino acids 1-117, and comprising or consisting essentially of fragments of nucleic acids coding for amino acids 1-117. Polypeptides
20 encoded by these nucleic acids are also claimed, including polypeptide fragments of 1-117, such as 1-23, 79-97, 164-198, 261-274, and other extracellularly exposed peptides. In addition, the present invention relates to binding partners, such as antibodies, that bind to epitopes within amino acids 1-117 (e.g., SEQ ID NO 153).

25 Pancreas

Diabetes and other pancreatic disorders are a major health concern. Worldwide, it is estimated that 5-10% of the population suffers from some form of diabetes. Pancreatic cancer is the fifth leading cause of cancer-related mortality. In 2002, it was estimated that about 30,000 Americans would be diagnosed with pancreatic cancer, and 90% would die
30 within 12 months. Despite the prevalence of pancreatic disease, the genetics and physiology of normal pancreatic function and pancreatic disease is still poorly understood.

The pancreas is a mixed gland comprised of exocrine and endocrine tissues. The exocrine portion comprises about 80-85% of the organ. It is divided into lobes by connective tissue septa, and each lobe is divided into several lobules. These lobules are composed of grape-like clusters of secretory cells that form sacs known as acini. An acinus is a functional unit of the pancreatic exocrine gland. All acini drain into interlobular ducts which merge to form the main pancreatic duct. It, in turn, joins together with the bile duct from the liver to form the common bile duct that empties into the duodenum. Pancreatic acinar cells make up more than 80% of the total volume of the pancreas and function in the secretion of the various enzymes that assist digestion in the gastrointestinal tract. Scattered among the acinar cells are approximately a million pancreatic islets ("islets of Langerhans") that secrete the pancreatic endocrine hormones. These dispersed islets comprise approximately 2% of the total volume of the pancreas.

The basic function of the pancreatic endocrine cells is to secrete certain hormones that participate in the metabolism of proteins, carbohydrates, and fats. The hormones secreted by the islets include, e.g., insulin, glucagon, somatostatin, pancreatic polypeptide, amylin, adrenomedullin, gastrin, secretin, and peptide-YY. See, also, Shimizu et al., *Endocrin.*, 139:389-396, 1998. The islets contain about four major and two minor cell types. The major cell types are alpha (glucagon producing), beta (insulin and amylin producing), delta (somatostatin producing which suppresses both insulin and glucagon release), and F (pancreatic polypeptide and adrenomedullin producing) cells. The minor cell types are D1 (produce vasoactive intestinal peptide or VIP) and enterochromaffin (produce serotonin) cells. The cells can be distinguished, e.g., by their morphology, hormonal content, and polynucleotide expression patterns.

The ability of the pancreas to respond to a wide variety of metabolic signals is conferred by an expression profile comprising a rich assortment of receptor proteins. G-protein coupled receptors have been previously identified in the pancreas, including, e.g., receptors for glucagon, secretin, CCK (e.g., Roettger et al., *J. Cell Biol.*, 130:579-590, 1995), purines (e.g., P2 purinoreceptors), gastrin, KiSS-1 peptides (e.g., Kotani et al., *J. Biol. Chem.*, 276:34631-6, 2001), adrenomedullin (Martinez et al., *Endocrin.*, 141:406, 2000), and interleukins. G-protein subunits have also been localized to the pancreas, including G-proteins which were previously associated with the olfactory epithelium. See, e.g., Zigman et

al., *Endocrin.*, 133:2508-2514, 1993. In addition, pancreatic cells express neurotropin, neurotensin, and interleukin receptors.

As mentioned, the pancreas is sensitive to a variety of metabolic, soluble and hormonal signals involved in regulating blood sugar, modulating synthesis and release of pancreatic digestive enzymes, and other physiologically important processes involved in pancreas function. In analogy to the ability of olfactory receptors to detect odors and pheromones in the environment, the pancreatic GPCRs of the present invention can be used to "sniff" out and respond to various ligands in the blood which pass through the pancreas, including peptides, metabolites, and other biologically-active molecules. Biological activities include, but are not limited to, e.g., regulation of blood sugar, modulation of all aspects of the various secreted polypeptides (hormones, enzymes, etc.) produced by the pancreas, ligand-binding, exocytosis, amylase (and any of the other 20 or so digestive enzymes produced by the pancreas) secretion, autocrine responses, apoptosis (e.g., in the survival of beta-islet cells), zymogen granule processing, G-protein coupling activity, etc.

The polynucleotides, polypeptides, and ligands thereto, of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of pancreas. These include, but are not limited to, e.g., disorders associated with loss or mutation to 11q24, such as Jacobsen syndrome (OMIM #147791), cystic fibrosis, acute and chronic pancreatitis, pancreatic abscess, pancreatic pseudocyst, nonalcoholic pancreatitis, alcoholic pancreatitis, classic acute hemorrhagic pancreatitis, chronic calcifying pancreatitis, familial hereditary pancreatitis, carcinomas of the pancreas, primary (idiopathic) diabetes (e.g., Type I (insulin dependent diabetes mellitus, IDDM) [insulin deficiency, beta cell depletion], Type II (non-insulin dependent diabetes mellitus, NIDDM) [insulin resistance, relative insulin deficiency, mild beta cell depletion]), nonobese NIDDM, obese NIDDM, maturity-onset diabetes of the young (MODY), islet cell tumors, diffuse hyperplasia of the islets of Langerhans, benign adenomas, malignant islet tumors, hyperfunction of the islets of Langerhans, hyperinsulinism and hypoglycemia, Zollinger-Ellison syndrome, beta cell tumors (insulinoma), alpha cell tumors (glucagonoma), delta cell tumors (somatostatinoma), vipoma (diarrheogenic islet cell tumor), pancreatic cancers, pancreatic carcinoid tumors, multihormonal tumors, multiple endocrine neoplasia (MEN), MEN I (Wermer syndrome), MEN II (Sipple syndrome), MEN III or IIb, pancreatic endocrine

tumors, etc.

In view of its selectivity and display on the cell surface, the olfactory GPCR family members of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., pancreatic progenitor, exocrine, endocrine, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies to identify bone marrow, lymphocytes, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 14. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The present invention relates to methods of detecting pancreas cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene of Table 12, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and

technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 154, 155, 164, 165, 169, 170, 173, 174, 177, and 178, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,
5 monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a pancreas cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by a polypeptide of Table 12, or a
10 mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 14.

As indicated above, binding partners can be used to deliver agents specifically to the
15 pancreas, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a pancreas cell can comprise, e.g., contacting a pancreas cell with an agent coupled to a binding partner specific for a polypeptide coding for a gene of Table 12, whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the pancreas can be achieved in any effective manner,
20 including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target),
25 present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by a gene of Table 12 can be targeted, including, e.g., pancreatic progenitor, exocrine, endocrine, secretory, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.

30 Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body.

Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose. See, Bruehlmeier et al., *Nucl. Med. Biol.*, 29:321-327, 2002, for imaging pancreas using labeled receptor ligands. Antibodies and other ligands to receptors of the present invention can be used analogously.

A pancreas cell (see above for examples of pancreas cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a pancreas cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene of Table 12, or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NO 153, 163, 168, 172, or 176), or a mammalian homolog thereof, whereby said pancreas cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

An activity or function of the pancreas cell can be modulated, including, e.g., regulation of blood sugar, modulation of all aspects of the various secreted polypeptides (hormones, enzymes, etc.) produced by the pancreas, ligand-binding, exocytosis, amylase (and any of the other 20 or so digestive enzymes produced by the pancreas) secretion, autocrine responses, apoptosis (e.g., in the survival of beta-islet cells), etc.

The present invention also relates to polypeptide detection methods for assessing pancreas function, e.g., methods of assessing pancreas function, comprising, detecting a polypeptide coded for by a gene of Table 12, fragments thereof, polymorphisms thereof, in a body fluid, whereby the level of said polypeptide in said fluid is a measure of pancreas function. Pancreas function tests are usually performed to determine whether the pancreas is functioning normally as a way of diagnosing pancreas disease. Various tests are commonly used, including, e.g., assays for the presence of pancreatic enzymes in body fluids (e.g.,

amylase, serum lipase, serum trypsin-like immuoreactivity), studies of pancreatic structure (e.g., using x-ray, sonography, CT-scan, angiography, endoscopic retrograde cholangiopancreatography), and tests for pancreatic function (e.g., secretin-pancreozymin (CCK) test, Lundh meal test, Bz-Ty-PABA test, chymotrypsin in feces, etc). Detection of a polypeptide coded for by a gene of Table 12 provides an additional assessment tool, especially in diseases such as pancreatitis and pancreatic cancer where pancreatic markers can appear in the blood, stool, urine, and other body fluids. As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired pancreas function. Values can be determined routinely, as they are for other markers, such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc., in analogy to the tests for pancreatic enzymes in body fluids.

Promoter sequences obtained from GPCR genes of the present invention can be utilized to selectively express heterologous genes in pancreas cells. Methods of expressing a heterologous polynucleotide in pancreas cells can comprise, e.g., expressing a nucleic acid construct in pancreas cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NOS 156-161, 166, 179, or 180. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

The genes and polypeptides of Table 12 can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the pancreas as mentioned above. The present invention relates to methods of identifying a pancreatic disease or pancreatic disease-susceptibility, comprising, e.g., determining the association of a pancreatic disease or pancreatic disease-susceptibility with a nucleotide sequence present within the pancreatic gene complex. An association between a pancreas disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target.

Any region of the pancreatic gene complex can be used as a source of the DNA marker (e.g., a nucleotide sequence present with PGC), including, e.g., TMD0986,

XM_061780 (TMD0987), XM_061781 (TMD0353), XM_061784 (TMD0989), XM_061785 (TMD058), and any part thereof, introns, intergenic regions, any DNA from about 29160-29310 kb of 11q24, NT_009215, etc.

Human linkage maps can be constructed to establish a relationship between a region within 11q24 and a pancreatic disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the various individual molecular markers. Maps can be produced individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identify the gene responsible for the phenotype.

Retina Selective Gene

The present invention relates to NM_013941 (GPCR181 or OR10C1), a multiple transmembrane spanning polypeptide which shares sequence identity with the olfactory G-protein coupled receptor (GPCR) family. Like other GPCR, NM_013941 has seven transmembrane domains, at about amino acid positions 20-42, 54-76, 91-113, 134-156, 190-212, 233-255, and 265-287, of SEQ ID NO 182. It is located at about chromosomal band 6p21.31-22.2. There are several other GPCRs located nearby (e.g., OR2B3, AL022727; OR2J3, AL022727). NM_013941 is highly expressed in brain tissue, at lower levels in heart, pituitary, and skin, and at minimally detectable levels in colon, small intestine, kidney, lymphocytes, and mammary gland. In the neuronal tissue, it was selectively expressed in the retina, but was not detected in any other brain tissue regions. The selective expression of NM_013941 in the retina makes it useful as a marker for retinal tissue, e.g., in stem cell cultures and biopsy samples, as well as a diagnostic, prognostic, therapeutic, and research tool for any conditions, diseases, disorders, or applications associated with the retina and the cells in which it is expressed. NM_013941 includes both human and mammalian homologs of it (e.g., mouse XM_111729 which is similar to olfactory receptor MOR263-6). SEQ ID NOS. 181 and 182 represent a particular allele of NM_013941; the present invention relates to other alleles, as well, including naturally-occurring polymorphisms (i.e., a polymorphism in the nucleotide sequence which is identified in populations of mammals).

The chromosomal region within which NM_013941 is located comprises a number of genes involved in retinal function. These include, e.g., retinal cone dystrophy (OMIM 602093) which appears to be a result of mutation in guanylate cyclase activator-1A (e.g., Payne et al., *Human Molec. Genet.*, 7:273-277, 1998), retinal degeneration slow (OMIM 179605) which appears to be a defect in specific retinal protein homologous to rod outer segment protein-1, retinitis pigmentosa-7, retinitis pigmentosa-14 (OMIM 600132) which is associated with a mutation in the tubby-like protein TULP1 (e.g., Banerjee et al., *Nature Genet.*, 18:177-179, 1998; Hagstrom et al., *Nature Genet.*, 18:174-176, 1998), and others. Thus, this region appears to be important in eye function.

In view of its selectivity and display on the cell surface, the olfactory GPCR family members of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to retinal cells. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat retinal carcinomas (e.g., retinoblastoma) in analogy to how c-erbB-2 antibodies are used to breast cancer. See, e.g., Hayashi et al., *Invest. Ophthalmol. Vis. Sci.*, 40:265-72, 1999 for an example treating retinoblastoma using HSV-TK. Transfer of the gene into the retinal cells can be achieved by incorporating the gene into liposomes which have been made cell-selective by incorporating a NM_013941 specific antibody into its bilayer. See, also, Wu and Wu, *J. Biol. Chem.*, 262: 4429-4432, 1987.

The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule

comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The present invention relates to methods of detecting retinal cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for NM_013941 (e.g., SEQ ID NOS 181), or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 183 and 184, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a retinal cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by NM_013941 (e.g., SEQ ID NO 182), or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface.

As indicated above, binding partners can be used to deliver agents specifically to the retina, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a retinal cell can comprise, e.g., contacting a retinal cell with an agent coupled to binding partner specific for NM_013941 (SEQ ID NO 182), whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the retinal can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent

is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by NM_013941 can be targeted, including, e.g., pigmented epithelial cells, photoreceptor cells, cones, rods, bipolar cells, ganglion cells, etc.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body.

Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

A retinal cell (see above for examples of retinal cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a retinal cell, comprising, e.g., contacting said cell with an agent effective to modulate NM_013941, or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NO 182), or a mammalian homolog thereof, whereby said retinal cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

Any activity or function of the retinal cell can be modulated, including, e.g., light reception, phototransduction, excitation of rods, excitation of cones, metabolism of vitamin A, retinal, rhodopsin, and other functional molecules, cGMP binding and hydrolysis, sodium channel flux, membrane potential, phosphodiesterase activity, G-protein activity and coupling, vitamin A processing, sodium pump activity, calcium flux, etc. The response of a retinal cell to stimuli can also be modulated, including, but not limited to, ligands to

NM_013941, light, ion levels, second messenger levels, etc.

Promoter sequences can be utilized to selectively express heterologous genes in retinal cells. Methods of expressing a heterologous polynucleotide in retinal cells can comprise, e.g., expressing a nucleic acid construct in retinal cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is obtained from NM_01394, e.g., on genomic NT_007592. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

10 Retina

The retina is a two-layered structure located on the back of the eye. It is the primary organ responsible for vision. The outer pigmented layer is comprised of pigmented epithelial cells that absorb light, preventing it from scattering in the eye, and store vitamin A needed by the photoreceptor cells. The inner neural layer is comprised of three main cell types:

15 photoreceptor cells, bipolar cells, and ganglion cells. The local currents generated by a light stimulus spreads from the photoreceptor cells to the bipolar cells, and then on to the innermost ganglion cells. The optic disc is the exit site of the retinal ganglion axons which then bundle into the optic nerve

Photoreceptors consist of rods and cones which are the photosensitive cells of the retina. Each rod and cone elaborates a specialized cilium, called the outer segment, that contains the phototransduction machinery. The rods contain a specific light-absorbing visual pigment, rhodopsin. In humans, there are three classes of cones, each characterized by the expression of distinct visual pigments: the blue cone, green cone and red cone pigments. Each type of visual pigment protein is tuned to absorb light maximally at different wavelengths. The rod rhodopsin mediates scotopic vision (in dim light), whereas the cone pigments are responsible for photopic vision (in bright light). The red, blue and green pigments also form the basis of color vision.

NM_013941 can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the retinal. These include, but are not limited to, diseases that affect the basic morphologic components as mentioned above, e.g., the outer and inner cell layers, and the optic nerve the retina. Diseases include, e.g.,

retinal degeneration, retinal degenerations such as retinitis pigmentosa, Bardet-Biedl syndrome, Bassen-Kornzweig syndrome (abetalipoproteinemia), Best disease (vitelliform dystrophy), choroidemia, gyrate atrophy, congenital amaurosis, Refsum syndrome, Stargardt disease, Usher syndrome, macular degeneration (dry and wet forms), diabetic retinopathy, peripheral vitreoretinopathies, photic retinopathies, surgery-induced retinopathies, viral retinopathies (such as HIV retinopathy related to AIDS), ischemic retinopathies, retinal detachment, traumatic retinopathy, optic neuropathy, optic neuritis, ischemic optic neuropathy, Leber optic neuropathy, diseases of Bruch's membrane, glaucoma, cancer, retinoblastoma, cancer-associated retinopathy syndrome (CAR syndrome), melanoma-associated retinopathy (MAR), etc. NM_013941 can also be used for staging and classifying conditions and diseases of the present invention, alone, or in combination with conventional staging and classification schemes.

Spleen Gene Cluster

The present invention relates to a cluster of transmembrane and GPCR-type receptor genes located at chromosomal band 11q12.2. The genes of the present invention are expressed predominantly in the spleen (e.g., Fig. 10, lane 19) (hence, "spleen gene" cluster), as well as other tissues of the immune and reticuloendothelial system (RES), establishing this region of the chromosome as a unique gene complex involved in spleen, lymphoid, and/or reticuloendothelial function. TMD1030 and TMD0621 are highly expressed in spleen tissue, with insignificant levels in other tissues. In addition to spleen. TMD1029 and TMD1029 show significant expression in the liver and lymphocytes, as well. Because of their selectivity for spleen, lymphoid, and/or reticuloendothelial tissues, the gene complex, and the chromosomal region which comprises it, are useful to assess spleen, lymphoid, and/or reticuloendothelial tissue function and for diagnostic, prognostic, therapeutic, and research purposes. Information on the genes is summarized in Tables 15-19.

The spatial organization of the gene complex is illustrated in Fig. 11. The complex spans about at least 100 kb, from about EST markers G62658, SHGC-82134, etc. (located at the end closest to the centromere and TMD1030) to SHGC-154002, SHGC-9433, etc. (located at the end furthest from the centromere and TMD0621). All the genes have the same orientation of transcription. TMD1799 (XM_166849) (SEQ ID NO 193-194), located at the

upper region, shows very high expression in lymphocytes, but only marginal expression in spleen, indicating that expression in lymphocytes may predominate at the boundaries of the gene complex. In the lower region, TMD1027 (XM_166856) (SEQ ID NO 195-196), spleen expression virtually disappears, while lymph node expression becomes very high. The

5 present invention includes this entire region, and any parts thereof. For instance, the present invention includes any DNA fragments within it which confer the observed tissue specificities described herein.

The gene complex is involved in spleen, immune, and RES functions. The spleen is located in the left upper region of the abdomen. In the adult, it weights about 90-180 grams, and is about 15
10 by 7.5 cm in size. The spleen is anatomically and functionally compartmentalized into two distinct regions, the red and white pulp. The red pulp comprises blood vessels interwoven with connective tissue ("pulp cords") that is lined with reticuloendothelial cells. It possesses a blood filtering function, removing opsonized cells and trapping abnormal red blood cells. It also is a storage reservoir for platelets and other blood cells. In the fetus, the red pulp has a hematopoietic function.

15 Inside the red pulp, is lymphoid tissue know as the white pulp. Antibodies are made inside the white pulp. Similar to other lymphatic tissues, B- and T-cell's mature inside the white pulp, where they are involved in antigen presentation and lymphocyte maturation. The white pulp is clustered around the periarteriolar lymphoid sheath, and is comprised of follicles and marginal zone.

Naive B-cells are located in the primary follicle, memory cells, macrophages, and dendritic cells
20 in the secondary follicle, and macrophages and B-cells in the marginal zone. The integrins LFA-1 and alpha4-beta1 are involved in localization of the B-cells to the marginal zone of the white pulp (Lu and Cyster, *Science*, 297:409, 2002).

The reticuloendothelial system (RES) is a multi-organ phagocytic system involved in removing particulates from the blood. It is comprised of the spleen and liver. It has the
25 ability to sequester inert particles and dyes. Cells of the RES system include, macrophages, liver Kuppfer cells, endothelial cells lining the sinusoids of the liver, spleen, and bone marrow, and reticular cells of lymphatic and bone marrow tissues.

The polynucleotides, polypeptides, and ligands thereto, of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc.,
30 diseases and conditions of spleen, lymphoid, and/or reticuloendothelial tissues. These include, but are not limited to, splenomegaly, hypersplenism, hemolytic anemis, hereditary

spherocytosis, hereditary eliptocytosis, thalassemia minor and major, autoimmune hemolytic anemia, thrombocytopenia, idiopathic thrombocytopenic purpura, immunologic thrombocytopenia associated with chronic lymphocytic leukemia or systemic lupus erythematosus, TTP, leukemia, lymphoma, primary and metastatic tumors, splenic cysts, infection, inflammatory diseases, anemias, blood cancers, etc. See, Table 19 for other examples.

In view of their selectivity and display on the cell surface, the genes of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., reticuloendothelial cells, macrophages, Kupffer cells, monocytes, B-lymphocytes, T-lymphocytes, etc) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to treat breast cancer. They can also be used to detect metastatic cells in biopsies. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly. See, Table 16. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types. TMD1030 and TMD0621 are predominantly and selectively expressed in spleen tissue.

The expression patterns of the selectively expressed polynucleotides disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by a tissue. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of expressed sequences disclosed herein provides an example of such a tissue expression profile. It can be used as a point of reference to compare and characterize samples. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue, to determine the origin of metastatic cells, to assess the physiological status of a tissue, to determine the effect of a particular treatment regime on a tissue, to evaluate the toxicity of a compound on a tissue of interest, etc.

For example, the tissue-selective polynucleotides disclosed herein represent the configuration of genes expressed by a normal tissue. To determine the effect of a toxin on a tissue, a sample of tissue can be obtained prior to toxin exposure ("control") and then at one or more time points after toxin exposure ("experimental"). An array of tissue-selective probes can be used to assess the expression patterns for both the control and experimental samples. As discussed in more detail below, any suitable method can be used. For instance, a DNA microarray can be prepared having a set of tissue-selective genes arranged on to a small surface area in fixed and addressable positions. RNA isolated from samples can be labeled using reverse transcriptase and radioactive nucleotides, hybridized to the array, and then expression levels determined using a detection system. Several kinds of information can be extracted: presence or absence of expression, and the corresponding expression levels. The normal tissue would be expected to express substantially all the genes represented by the tissue-selective probes. The various experimental conditions can be compared to it to determine whether a gene is expressed, and how its levels match up to the normal control.

While the expression profile of the complete gene set represented by the sequences disclosed here may be most informative, a fingerprint containing expression information from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, because of heterogeneity of the population, as well differences in the particular physiological state of the tissue, a tissue's "normal" expression profile is expected to differ

between samples, albeit in ways that do not change the overall expression pattern. As a result of these individual differences, each gene although expressed selectively in spleen, may not on its own 100% of the time be adequately enough expressed to distinguish said tissue.

Thus, the genes can be used in any of the methods and processes mentioned above and below as a group, or one at a time.

The present invention relates to methods of detecting spleen, lymphoid, and/or reticuloendothelial cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 197-204 listed in Table 17, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a spleen, lymphoid, and/or reticuloendothelial cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by a polypeptide of the present invention, or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface. Detection can be useful for assessing spleen integrity, e.g., when it is suspected that the spleen is damaged and undergoing deterioration. The appearance of polypeptides of the present invention in body fluids, such as blood, can indicate spleen damage, including neoplastic and/or apoptotic changes.

As indicated above, binding partners can be used to deliver agents specifically to the spleen, lymphoid, and/or reticuloendothelial tissues, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a spleen, lymphoid, and/or

reticuloendothelial cell can comprise, e.g., contacting a spleen, lymphoid, and/or reticuloendothelial cell with an agent coupled to a binding partner specific for a polypeptide coding for TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), whereby said agent is delivered to said cell. Any type of agent can
5 be used, including, therapeutic and imaging agents. Contact with the spleen, lymphoid, and/or reticuloendothelial tissue can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parenterally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried
10 specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by TMD1030 (XM_166853),
15 TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205) can be targeted, including, e.g., reticuloendothelial cells, macrophages, Kupffer cells, lymphocytes, B-lymphocytes, T-lymphocytes, etc.

Antibodies (alone or conjugated to active agents) can be used to ablate spleen and other tissues. For instance, in diseases where splenectomy is indicated (e.g., immune
20 thrombocytopenic purpura, autoimmune hemolytic anemia, blood cell disorders, myeloproliferative disorders, tumors, hypersplenism, etc.), antibodies to TMD1030 and TMD0621 can be used to ablate spleen tissue, or block spleen function.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body.
25 Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic imaging. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos, 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal
30 chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The

methods described therein can be used generally to associate a partner with an agent for any desired purpose. See, Bruehlmeier et al., *Nucl. Med. Biol.*, 29:321-327, 2002, for imaging using labeled receptor ligands. Antibodies and other ligands to receptors of the present invention can be used analogously.

5 A cell (see above for examples of spleen, lymphoid, and/or reticuloendothelial cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a spleen, lymphoid, and/or reticuloendothelial cell, comprising, e.g., contacting said cell with an agent effective to modulate TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), or the biological
10 activity of a polypeptide encoded thereby (e.g., SEQ ID NOS 185-192), or a mammalian homolog thereof, whereby said spleen, lymphoid, and/or reticuloendothelial cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

15 Any activity or function of the spleen, lymphoid, and/or reticuloendothelial tissues can be modulated, including, e.g., immune modulation (e.g., modulating antigen presentation, antibody production and secretion, humoral and cellular responses, etc.), sequestration and removal of red blood cells, clearance of microorganisms and particular antigens from blood, migration into the marginal zone or other immune and RES compartments, etc.

20 The present invention also relates to polypeptide detection methods for assessing spleen, lymphoid, and/or reticuloendothelial tissue function, e.g., methods of assessing spleen, lymphoid, and/or reticuloendothelial function, comprising, detecting a polypeptide coded for by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), fragments thereof, polymorphisms thereof, in a body fluid,
25 whereby the level of said polypeptide in said fluid is a measure of spleen, lymphoid, and/or reticuloendothelial function. spleen, lymphoid, and/or reticuloendothelial function tests are usually performed to determine whether the spleen, lymphoid, and/or reticuloendothelial tissue is functioning normally as a way of diagnosing spleen, lymphoid, and/or reticuloendothelial disease. Various tests are commonly used, including, e.g., ⁹⁹Tc-colloid
30 liver-spleen scan, computed tomography, ultrasound scanning of left upper quadrant, MRI, liver enzymes, etc.

Detection of a polypeptide coded for by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), provides an additional assessment tool, especially in diseases or disorders, such as splenomegaly, hypersplenism, or ruptured spleen, where said polypeptides can appear in the blood, stool, urine, and other body fluids. As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired spleen, lymphoid, and/or reticuloendothelial function. Values can be determined routinely, as they are for other markers, such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc., in analogy to the tests for enzymes and other proteins in body fluids.

Promoter sequences obtained from genes of the present invention can be utilized to selectively express heterologous genes in cells. Methods of expressing a heterologous polynucleotide in cells, e.g., spleen, lymphoid, and/or reticuloendothelial cells can comprise, e.g., expressing a nucleic acid construct in spleen, lymphoid, and/or reticuloendothelial cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NOS 205-213. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

The genes and polypeptides of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the spleen, lymphoid, and/or reticuloendothelial tissues mentioned above. The present invention relates to methods of identifying a genetic basis for a disease or disease-susceptibility, comprising, e.g., determining the association of a spleen, lymphoid, and/or reticuloendothelial disease or spleen, lymphoid, and/or reticuloendothelial disease-susceptibility with the gene complex of the present invention, e.g., a nucleotide sequence present in the gene complex at 11q12.2. An association between a spleen, lymphoid, and/or reticuloendothelial disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target.

Any region of the gene can be used as a source of the DNA marker, exons, introns,

intergenic regions, or any DNA from the gene cluster of the present invention at chromosomal region 11q12.2, etc.

Human linkage maps can be constructed to establish a relationship between a gene and a spleen, lymphoid, and/or reticuloendothelial disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the various individual molecular markers. Maps can be produced for an individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identify the gene responsible for the phenotype.

The present invention also relates to methods of expressing a polynucleotide in spleen, lymphoid, and/or reticuloendothelial tissue, comprising, e.g., inserting a polynucleotide, which is operably linked to an expression control sequence, into the spleen, lymphoid, and/or reticuloendothelial gene complex at chromosomal location 11q12.2 of a target cell, and growing said cell under conditions effective to express said polynucleotide.

The polynucleotide of interest can be inserted into the target chromosomal region by any suitable method, including, e.g., by gene targeting methods, such as homologous recombination, or by random insertion methods where transformed cells are subsequently screened for insertion into the desired chromosomal site. Chromosome engineering methods are discussed in more detail below, e.g., in the section on transgenic animals. By the phrase "spleen, lymphoid, and/or reticuloendothelial gene complex," it is meant the region of the chromosome in which the cluster of genes, e.g., TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), and TMD0621 (XM_166205), of the present invention are located. Inserting an expressible polynucleotide (e.g., a polynucleotide operably linked to a promoter sequence) into this region confers the tissue expression selectivity which is characteristic of the gene cluster. Any polynucleotide of interest can be inserted into the chromosomal region, including, e.g., polynucleotides encoding polypeptides, antisense polynucleotides, etc.

A cell comprising a polynucleotide inserted into the target chromosomal location can be utilized in vitro or in vivo, e.g., in a transgenic animal. The cell is grown under conditions

which are suitable to achieve polynucleotide expression. These conditions depend upon the cell's environment, e.g., tissue culture cell, or in the form of a transgenic animal.

Pancreas membrane protein genes

5 The present invention relates to all facets of pancreas membrane protein genes, polypeptides encoded by them, antibodies and specific binding partners thereto, and their applications to research, diagnosis, drug discovery, therapy, clinical medicine, forensic science and medicine, etc. The polynucleotides and polypeptides are useful in variety of ways, including, but not limited to, as molecular markers, as drug targets, and for detecting, 10 diagnosing, staging, monitoring, prognosticating, preventing or treating, determining predisposition to, etc., diseases and conditions, such as pancreatic cancer, diabetes, pancreatitis, and other disorders especially relating to the pancreas and the functions its performs. The identification of specific genes, and groups of genes, expressed in pathways physiologically relevant to pancreas tissue permits the definition of functional and disease 15 pathways, and the delineation of targets in these pathways which are useful in diagnostic, therapeutic, and clinical applications. The present invention also relates to methods of using the polynucleotides and related products (proteins, antibodies, etc.) in business and computer-related methods, e.g., advertising, displaying, offering, selling, etc., such products for sale, commercial use, licensing, etc.

20 The function, structure, and diseases of the pancreas were described previously. The polynucleotides, polypeptides, and ligands thereto, of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of pancreas. These include, but are not limited to, e.g., acute and chronic pancreatitis, pancreatic abscess, pancreatic pseudocyst, nonalcoholic pancreatitis, alcoholic 25 pancreatitis, classic acute hemorrhagic pancreatitis, chronic calcifying pancreatitis, familial hereditary pancreatitis, carcinomas of the pancreas, primary (idiopathic) diabetes (e.g., Type I (insulin dependent diabetes mellitus, IDDM) [insulin deficiency, beta cell depletion], Type II (non-insulin dependent diabetes mellitus, NIDDM) [insulin resistance, relative insulin deficiency, mild beta cell depletion]), nonobese NIDDM, obese NIDDM, maturity-onset 30 diabetes of the young (MODY), islet cell tumors, diffuse hyperplasia of the islets of Langerhans, benign adenomas, malignant islet tumors, hyperfunction of the islets of Langerhans, hyperinsulinism and hypoglycemia, Zollinger-Ellison syndrome, beta cell

tumors (insulinoma), alpha cell tumors (glucagonoma), delta cell tumors (somatostatinoma), vipoma (diarrheogenic islet cell tumor), pancreatic cancers, pancreatic carcinoid tumors, multihormonal tumors, multiple endocrine neoplasia (MEN), MEN I (Wermer syndrome), MEN II (Sipple syndrome), MEN III or IIb, pancreatic endocrine tumors, etc.

5 For example, five different pancreatic tumor samples were examined (Nos. 1, 2, 3, 4, and 5). TMD0639 was up-regulated in about 1/5 pancreatic cancers (No. 4), TMD0645 was up-regulated in about 3/5 pancreatic cancers (Nos. 2, 3, and 5), and TMD1127 was up-regulated in about 2/5 pancreatic cancers (Nos. 1 and 4). These results indicate that the probes can be used in combination in order to maximize the detection of different types of
10 pancreatic cancers and tumors. Thus, a sample from a patient can be assessed for expression of both TMD0645 and TMD1127 to increase the probability that the pancreas cancer will be detected.

In view of their selectivity and display on the cell surface, the membrane proteins of the present invention are useful targets for histological, diagnostic, and therapeutic
15 applications relating to the cells (e.g., pancreatic progenitor, exocrine, endocrine, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such
20 as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells in biopsies and other tissue samples. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or
25 other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 21. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other
30 tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule

comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

Table 20 is a summary of the genes of the present invention which are expressed selectively and/or predominantly in pancreas tissue. Fig. 12 is an illustration of these expression patterns. Each gene is associated with a Clone ID and Accession Number ("ACCN"). The Clone ID is an arbitrary identification number for the clone, and the accession number is the number by which it is listed in GenBank. Although specific sequences are disclosed herein, and listed in GenBank by an accession number), the present invention includes all forms of the gene, including polymorphisms, allelic variations, SNPs, splice variants, and any full-length versions when the disclosed or Genbank version is partial. For convenience, these genes, and their homologs in other species, are referred to throughout the disclosure in shorthand as "the genes of Table 20," "a gene of Table 20," "polynucleotides of Table 20," "polypeptides of Table 20," etc., because Table 20 contains a listing of the genes by accession number and clone ID.

The expression patterns of the selectively and/or predominantly expressed polynucleotides disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by pancreas tissue. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of expressed sequences disclosed herein provides an example of such a tissue expression profile. It can be used as a point of reference to compare and characterize samples. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue, to determine the origin of metastatic cells, to assess the physiological status of a tissue, to determine the effect of a particular treatment regime on a tissue, to evaluate the toxicity of a compound on a tissue of interest, etc.

For example, the pancreas-selective polynucleotides disclosed herein represent the configuration of genes expressed by a normal pancreas tissue. To determine the effect of a toxin on a tissue, a sample of tissue can be obtained prior to toxin exposure ("control") and then at one or more time points after toxin exposure ("experimental"). An array of pancreas-

selective probes can be used to assess the expression patterns for both the control and experimental samples. As discussed in more detail below, any suitable method can be used. For instance, a DNA microarray can be prepared having a set of pancreas-selective genes arranged on to a small surface area in fixed and addressable positions. RNA isolated from samples can be labeled using reverse transcriptase and radioactive nucleotides, hybridized to the array, and then expression levels determined using a detection system. Several kinds of information can be extracted: presence or absence of expression, and the corresponding expression levels. The normal tissue would be expected to express substantially all the genes represented by the tissue-selective probes. The various experimental conditions can be compared to it to determine whether a gene is expressed, and how its levels match up to the normal control.

While the expression profile of the complete gene set represented by the sequences disclosed here may be most informative, a fingerprint containing expression information from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, because of heterogeneity of the population, as well differences in the particular physiological state of the tissue, a tissue's "normal" expression profile is expected to differ between samples, albeit in ways that do not change the overall expression pattern. As a result, a complete match with a particular tissue expression profile, as shown herein, is not necessary.

The present invention relates to methods of detecting pancreas cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene of Table 20, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include the primer sequences shown in Table 23, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,

monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a pancreas cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by a polypeptide of Table 20, or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface.

As indicated above, binding partners can be used to deliver agents specifically to the pancreas, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a pancreas cell can comprise, e.g., contacting a pancreas cell with an agent coupled to a binding partner specific for a polypeptide coding for a gene of Table 20, whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the pancreas can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by a gene of Table 20 can be targeted, including, e.g., pancreatic progenitor, exocrine, endocrine, secretory, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917,

6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose. See, Bruehlmeier et al., *Nucl. Med. Biol.*, 29:321-327, 2002, for imaging pancreas using labeled receptor ligands. Antibodies and other ligands to receptors of the present invention can be used analogously.

A pancreas cell (see above for examples of pancreas cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a pancreas cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene of Table 20, or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NO 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, and 255), or a mammalian homolog thereof, whereby said pancreas cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

An activity or function of the pancreas cell can be modulated, including, e.g., regulation of blood sugar, modulation of all aspects of the various secreted polypeptides (hormones, enzymes, etc.) produced by the pancreas, ligand-binding, exocytosis, amylase (and any of the other 20 or so digestive enzymes produced by the pancreas) secretion, autocrine responses, apoptosis (e.g., in the survival of beta-islet cells), etc.

The present invention also relates to polypeptide detection methods for assessing pancreas function, e.g., methods of assessing pancreas function, comprising, detecting a polypeptide coded for by a gene of Table 20, fragments thereof, polymorphisms thereof, in a body fluid, whereby the level of said polypeptide in said fluid is a measure of pancreas function. Pancreas function tests are usually performed to determine whether the pancreas is functioning normally as a way of diagnosing pancreas disease. Various tests are commonly used, including, e.g., assays for the presence of pancreatic enzymes in body fluids (e.g., amylase, serum lipase, serum trypsin-like immunoreactivity), studies of pancreatic structure (e.g., using x-ray, sonography, CT-scan, angiography, endoscopic retrograde cholangiopancreatography), and tests for pancreatic function (e.g., secretin-pancreozymin

(CCK) test, Lundh meal test, Bz-Ty-PABA test, chymotrypsin in feces, etc). Detection of a polypeptide coded for by a gene of Table 20 provides an additional assessment tool, especially in diseases such as pancreatitis and pancreatic cancer where pancreatic markers can appear in the blood, stool, urine, and other body fluids. As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired pancreas function. Values can be determined routinely, as they are for other markers, such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc., in analogy to the tests for pancreatic enzymes in body fluids.

Promoter sequences obtained from genes of the present invention can be utilized to selectively express heterologous genes in pancreas cells. Methods of expressing a heterologous polynucleotide in pancreas cells can comprise, e.g., expressing a nucleic acid construct in pancreas cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NO 258, 261, 262, 265-267, 270-272, 275, 278, 279, 282-284, 287, 290-293, 296, 297, 303, 306, 309-314, 317-320, 323-326, 329, 332-333, 336-338, 341, and 344 as shown in Table 23. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

The genes and polypeptides of Table 20 can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the pancreas as mentioned above. The present invention relates to methods of identifying a pancreatic disease or pancreatic disease-susceptibility, comprising, e.g., determining the association of a pancreatic disease or pancreatic disease-susceptibility with a nucleotide sequence present within the pancreatic gene complex. An association between a pancreas disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target.

Human linkage maps can be constructed to establish a relationship between the cytogenetic locus as shown in Table 22 and a pancreatic disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified

within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the various individual molecular markers.

Maps can be produced individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g.,

- 5 identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identify the gene responsible for the phenotype.

Nucleic acids

- A mammalian polynucleotide, or fragment thereof, of the present invention is a
10 polynucleotide having a nucleotide sequence obtainable from a natural source. When the species name is used, e.g., a human, it indicates that the polynucleotide or polypeptide is obtainable from a natural source. It therefore includes naturally-occurring normal, naturally-occurring mutant, and naturally-occurring polymorphic alleles (e.g., SNPs), differentially-spliced transcripts, splice-variants, etc. By the term "naturally-occurring," it is meant that the
15 polynucleotide is obtainable from a natural source, e.g., animal tissue and cells, body fluids, tissue culture cells, forensic samples. Natural sources include, e.g., living cells obtained from tissues and whole organisms, tumors, cultured cell lines, including primary and immortalized cell lines. Naturally-occurring mutations can include deletions (e.g., a truncated amino- or carboxy-terminus), substitutions, inversions, or additions of nucleotide sequence. These
20 genes can be detected and isolated by polynucleotide hybridization according to methods which one skilled in the art would know, e.g., as discussed below.

- A polynucleotide according to the present invention can be obtained from a variety of different sources. It can be obtained from DNA or RNA, such as polyadenylated mRNA or total RNA, e.g., isolated from tissues, cells, or whole organism. The polynucleotide can be
25 obtained directly from DNA or RNA, from a cDNA library, from a genomic library, etc. The polynucleotide can be obtained from a cell or tissue (e.g., from an embryonic or adult tissues) at a particular stage of development, having a desired genotype, phenotype, disease status, etc.

- The polynucleotides described herein can be partial sequences that correspond to full-
30 length, naturally-occurring transcripts. The present invention includes, as well, full-length polynucleotides that comprise these partial sequences, e.g., genomic DNAs and polynucleotides comprising a start and stop codon, a start codon and a polyA tail, a

transcription start and a polyA tail, etc. These sequences can be obtained by any suitable method, e.g., using a partial sequence as a probe to select a full-length cDNA from a library containing full-length inserts. A polynucleotide which "codes without interruption" refers to a polynucleotide having a continuous open reading frame ("ORF") as compared to an ORF which is interrupted by introns or other noncoding sequences.

Polynucleotides and polypeptides can be excluded as compositions from the present invention if, e.g., listed in a publicly available databases on the day this application was filed and/or disclosed in a patent application having an earlier filing or priority date than this application and/or conceived and/or reduced to practice earlier than a polynucleotide in this application.

As described herein, the phrase "an isolated polynucleotide which is SEQ ID NO," or "an isolated polynucleotide which is selected from SEQ ID NO," refers to an isolated nucleic acid molecule from which the recited sequence was derived (e.g., a cDNA derived from mRNA; cDNA derived from genomic DNA). Because of sequencing errors, typographical errors, etc., the actual naturally-occurring sequence may differ from a SEQ ID listed herein. Thus, the phrase indicates the specific molecule from which the sequence was derived, rather than a molecule having that exact recited nucleotide sequence, analogously to how a culture depository number refers to a specific cloned fragment in a cryotube.

As explained in more detail below, a polynucleotide sequence of the invention can contain the complete sequence as shown herein, degenerate sequences thereof, anti-sense, mutants thereof, genes comprising said sequences, full-length cDNAs comprising said sequences, complete genomic sequences, fragments thereof, homologs, primers, nucleic acid molecules which hybridize thereto, derivatives thereof, etc.

Genomic

The present invention also relates genomic DNA from which the polynucleotides of the present invention can be derived. A genomic DNA coding for a human, mouse, or other mammalian polynucleotide, can be obtained routinely, for example, by screening a genomic library (e.g., a YAC library) with a polynucleotide of the present invention, or by searching nucleotide databases, such as GenBank and EMBL, for matches. Promoter and other regulatory regions (including both 5' and 3' regions, as well introns) can be identified

upstream or downstream of coding and expressed RNAs, and assayed routinely for activity, e.g., by joining to a reporter gene (e.g., CAT, GFP, alkaline phosphatase, luciferase, galactosidase). A promoter obtained from a tissue selective gene can be used, e.g., in gene therapy to obtain tissue-specific expression of a heterologous gene (e.g., coding for a therapeutic product or cytotoxin). 5' and 3' sequences (including, UTRs and introns) can be used to modulate or regulate stability, transcription, and translation of nucleic acids, including the sequence to which is attached in nature, as well as heterologous nucleic acids.

Constructs

A polynucleotide of the present invention can comprise additional polynucleotide sequences, e.g., sequences to enhance expression, detection, uptake, cataloging, tagging, etc. A polynucleotide can include only coding sequence; a coding sequence and additional non-naturally occurring or heterologous coding sequence (e.g., sequences coding for leader, signal, secretory, targeting, enzymatic, fluorescent, antibiotic resistance, and other functional or diagnostic peptides); coding sequences and non-coding sequences, e.g., untranslated sequences at either a 5' or 3' end, or dispersed in the coding sequence, e.g., introns.

A polynucleotide according to the present invention also can comprise an expression control sequence operably linked to a polynucleotide as described above. The phrase "expression control sequence" means a polynucleotide sequence that regulates expression of a polypeptide coded for by a polynucleotide to which it is functionally ("operably") linked. Expression can be regulated at the level of the mRNA or polypeptide. Thus, the expression control sequence includes mRNA-related elements and protein-related elements. Such elements include promoters, enhancers (viral or cellular), ribosome binding sequences, transcriptional terminators, etc. An expression control sequence is operably linked to a nucleotide coding sequence when the expression control sequence is positioned in such a manner to effect or achieve expression of the coding sequence. For example, when a promoter is operably linked 5' to a coding sequence, expression of the coding sequence is driven by the promoter. Expression control sequences can include an initiation codon and additional nucleotides to place a partial nucleotide sequence of the present invention in-frame in order to produce a polypeptide (e.g., pET vectors from Promega have been designed to permit a molecule to be inserted into all three reading frames to identify the one that results

in polypeptide expression). Expression control sequences can be heterologous or endogenous to the normal gene.

A polynucleotide of the present invention can also comprise nucleic acid vector sequences, e.g., for cloning, expression, amplification, selection, etc. Any effective vector can be used. A vector is, e.g., a polynucleotide molecule which can replicate autonomously in a host cell, e.g., containing an origin of replication. Vectors can be useful to perform manipulations, to propagate, and/or obtain large quantities of the recombinant molecule in a desired host. A skilled worker can select a vector depending on the purpose desired, e.g., to propagate the recombinant molecule in bacteria, yeast, insect, or mammalian cells. The following vectors are provided by way of example. Bacterial: pQE70, pQE60, pQE-9 (Qiagen), pBS, pD10, Phagescript, phiX174, pBK Phagemid, pNH8A, pNH16a, pNH18Z, pNH46A (Stratagene); Bluescript KS+II (Stratagene); ptrc99a, pKK223-3, pKK233-3, pDR54 0, pRIT5 (Pharmacia). Eukaryotic: PWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene), pSVK3, PBPV, PMSG, pSVL (Pharmacia), pCR2.1/TOPO, pCRII/TOPO, pCR4/TOPO, pTrcHisB, pCMV6-XL4, etc. However, any other vector, e.g., plasmids, viruses, or parts thereof, may be used as long as they are replicable and viable in the desired host. The vector can also comprise sequences which enable it to replicate in the host whose genome is to be modified.

Hybridization

Polynucleotide hybridization, as discussed in more detail below, is useful in a variety of applications, including, in gene detection methods, for identifying mutations, for making mutations, to identify homologs in the same and different species, to identify related members of the same gene family, in diagnostic and prognostic assays, in therapeutic applications (e.g., where an antisense polynucleotide is used to inhibit expression), etc.

The ability of two single-stranded polynucleotide preparations to hybridize together is a measure of their nucleotide sequence complementarity, e.g., base-pairing between nucleotides, such as A-T, G-C, etc. The invention thus also relates to polynucleotides, and their complements, which hybridize to a polynucleotide comprising a nucleotide sequence as set forth herein and genomic sequences thereof. A nucleotide sequence hybridizing to the latter sequence will have a complementary polynucleotide strand, or act as a template for one

in the presence of a polymerase (i.e., an appropriate polynucleotide synthesizing enzyme). The present invention includes both strands of polynucleotide, e.g., a sense strand and an anti-sense strand.

Hybridization conditions can be chosen to select polynucleotides which have a
5 desired amount of nucleotide complementarity with the nucleotide sequences set forth in
herein and genomic sequences thereof. A polynucleotide capable of hybridizing to such
sequence, preferably, possesses, e.g., about 70%, 75%, 80%, 85%, 87%, 90%, 92%, 95%,
97%, 99%, or 100% complementarity, between the sequences. The present invention
particularly relates to polynucleotide sequences which hybridize to the nucleotide sequences
10 set forth in the attached sequence disclosure or genomic sequences thereof, under low or high
stringency conditions. These conditions can be used, e.g., to select corresponding homologs
in non-human species.

Polynucleotides which hybridize to polynucleotides of the present invention can be
selected in various ways. Filter-type blots (i.e., matrices containing polynucleotide, such as
15 nitrocellulose), glass chips, and other matrices and substrates comprising polynucleotides
(short or long) of interest, can be incubated in a prehybridization solution (e.g., 6X SSC,
0.5% SDS, 100 µg/ml denatured salmon sperm DNA, 5X Denhardt's solution, and 50%
formamide), at 22-68°C, overnight, and then hybridized with a detectable polynucleotide
probe under conditions appropriate to achieve the desired stringency. In general, when high
20 homology or sequence identity is desired, a high temperature can be used (e.g., 65 °C). As
the homology drops, lower washing temperatures are used. For salt concentrations, the lower
the salt concentration, the higher the stringency. The length of the probe is another
consideration. Very short probes (e.g., less than 100 base pairs) are washed at lower
temperatures, even if the homology is high. With short probes, formamide can be omitted.
25 See, e.g., *Current Protocols in Molecular Biology*, Chapter 6, Screening of Recombinant
Libraries; Sambrook et al., *Molecular Cloning*, 1989, Chapter 9.

For instance, high stringency conditions can be achieved by incubating the blot
overnight (e.g., at least 12 hours) with a polynucleotide probe in a hybridization solution
containing, e.g., about 5X SSC, 0.1-0.5% SDS, 100 µg/ml denatured salmon sperm DNA and
30 50% formamide, at 42°C, or hybridizing at 42°C in 5X SSPE, 0.1-0.5% SDS, and 50%

formamide, 100 µg/ml denatured salmon sperm DNA, and washing at 65°C in 0.1% SSC and 0.1% SDS.

Blots can be washed at high stringency conditions that allow, e.g., for less than 5% bp mismatch (e.g., wash twice in 0.1% SSC and 0.1% SDS for 30 min at 65°C), i.e.,

- 5 selecting sequences having 95% or greater sequence identity.

Other non-limiting examples of high stringency conditions includes a final wash at 65°C in aqueous buffer containing 30 mM NaCl and 0.5% SDS. Another example of high stringent conditions is hybridization in 7% SDS, 0.5 M NaPO₄, pH 7, 1 mM EDTA at 50°C, e.g., overnight, followed by one or more washes with a 1% SDS solution at 42°C.

- 10 Whereas high stringency washes can allow for, e.g., less than 10%, less than 5% mismatch, etc., reduced or low stringency conditions can permit up to 20% nucleotide mismatch.

Hybridization at low stringency can be accomplished as above, but using lower formamide conditions, lower temperatures and/or lower salt concentrations, as well as longer periods of incubation time.

- 15 Hybridization can also be based on a calculation of melting temperature (T_m) of the hybrid formed between the probe and its target, as described in Sambrook et al.. Generally, the temperature T_m at which a short oligonucleotide (containing 18 nucleotides or fewer) will melt from its target sequence is given by the following equation: T_m = (number of A's and T's) x 2°C + (number of C's and G's) x 4°C. For longer molecules, T_m = 81.5 + 16.6
20 log₁₀[Na⁺] + 0.41(%GC) - 600/N where [Na⁺] is the molar concentration of sodium ions, %GC is the percentage of GC base pairs in the probe, and N is the length. Hybridization can be carried out at several degrees below this temperature to ensure that the probe and target can hybridize. Mismatches can be allowed for by lowering the temperature even further.

- Stringent conditions can be selected to isolate sequences, and their complements,
25 which have, e.g., at least about 90%, 95%, or 97%, nucleotide complementarity between the probe (e.g., a short polynucleotide of the sequences disclosed herein or genomic sequences thereof) and a target polynucleotide.

- Other homologs of polynucleotides of the present invention can be obtained from mammalian and non-mammalian sources according to various methods. For example,
30 hybridization with a polynucleotide can be employed to select homologs, e.g., as described in Sambrook et al., *Molecular Cloning*, Chapter 11, 1989. Such homologs can have varying

amounts of nucleotide and amino acid sequence identity and similarity to such polynucleotides of the present invention. Mammalian organisms include, e.g., mice, rats, monkeys, pigs, cows, etc. Non-mammalian organisms include, e.g., vertebrates, invertebrates, zebra fish, chicken, *Drosophila*, *C. elegans*, *Xenopus*, yeast such as *S. pombe*,
5 *S. cerevisiae*, roundworms, prokaryotes, plants, *Arabidopsis*, *artemia*, viruses, etc. The degree of nucleotide sequence identity between human and mouse can be about, e.g. 70% or more, 85% or more for open reading frames, etc.

Alignment

10 Alignments can be accomplished by using any effective algorithm. For pairwise alignments of DNA sequences, the methods described by Wilbur-Lipman (e.g., Wilbur and Lipman, *Proc. Natl. Acad. Sci.*, 80:726-730, 1983) or Martinez/Needleman-Wunsch (e.g., Martinez, *Nucleic Acid Res.*, 11:4629-4634, 1983) can be used. For instance, if the Martinez/Needleman-Wunsch DNA alignment is applied, the minimum match can be set at
15 9, gap penalty at 1.10, and gap length penalty at 0.33. The results can be calculated as a similarity index, equal to the sum of the matching residues divided by the sum of all residues and gap characters, and then multiplied by 100 to express as a percent. Similarity index for related genes at the nucleotide level in accordance with the present invention can be greater than 70%, 80%, 85%, 90%, 95%, 99%, or more. Pairs of protein sequences can be aligned
20 by the Lipman-Pearson method (e.g., Lipman and Pearson, *Science*, 227:1435-1441, 1985) with k-tuple set at 2, gap penalty set at 4, and gap length penalty set at 12. Results can be expressed as percent similarity index, where related genes at the amino acid level in accordance with the present invention can be greater than 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more. Various commercial and free sources of alignment programs are
25 available, e.g., MegAlign by DNA Star, BLAST (National Center for Biotechnology Information), BCM (Baylor College of Medicine) Launcher, etc. BLAST can be used to calculate amino acid sequence identity, amino acid sequence homology, and nucleotide sequence identity. These calculations can be made along the entire length of each of the target sequences which are to be compared.

30 After two sequences have been aligned, a "percent sequence identity" can be determined. For these purposes, it is convenient to refer to a Reference Sequence and a

Compared Sequence, where the Compared Sequence is *compared* to the Reference Sequence.

Percent sequence identity can be determined according to the following formula: Percent Identity = $100 [1 - (C/R)]$; wherein C is the number of differences between the Reference Sequence and the Compared Sequence over the length of alignment between the Reference Sequence and the Compared Sequence where (i) each base or amino acid in the Reference Sequence that does not have a corresponding aligned base or amino acid in the Compared Sequence, (ii) each gap in the Reference Sequence, (iii) each aligned base or amino acid in the Reference Sequence that is different from an aligned base or amino acid in the Compared Sequence, constitutes a difference; and R is the number of bases or amino acids in the Reference Sequence over the length of the alignment with the Compared Sequence with any gap created in the Reference Sequence also being counted as a base or amino acid.

Percent sequence identity can also be determined by other conventional methods, e.g., as described in Altschul et al., *Bull. Math. Bio.* 48: 603-616, 1986 and Henikoff and Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915-10919, 1992.

Specific polynucleotide probes

A polynucleotide of the present invention can comprise any continuous nucleotide sequence described herein, sequences which share sequence identity thereto, or complements thereof. The term "probe" refers to any substance that can be used to detect, identify, isolate, etc., another substance. A polynucleotide probe is comprised of nucleic acid can be used to detect, identify, etc., other nucleic acids, such as DNA and RNA.

These polynucleotides can be of any desired size that is effective to achieve the specificity desired. For example, a probe can be from about 7 or 8 nucleotides to several thousand nucleotides, depending upon its use and purpose. For instance, a probe used as a primer PCR can be shorter than a probe used in an ordered array of polynucleotide probes. Probe sizes vary, and the invention is not limited in any way by their size, e.g., probes can be from about 7-2000 nucleotides, 7-1000, 8-700, 8-600, 8-500, 8-400, 8-300, 8-150, 8-100, 8-75, 7-50, 10-25, 14-16, at least about 8, at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or more, etc. The polynucleotides can have non-naturally-occurring nucleotides, e.g., inosine, AZT, 3TC, etc. The polynucleotides can have 100% sequence identity or complementarity to a sequence disclosed herein, or it can have mismatches or

nucleotide substitutions, e.g., 1, 2, 3, 4, or 5 substitutions. The probes can be single-stranded or double-stranded.

In accordance with the present invention, a polynucleotide can be present in a kit, where the kit includes, e.g., one or more polynucleotides, a desired buffer (e.g., phosphate, tris, etc.), detection compositions, RNA or cDNA from different tissues to be used as controls, libraries, etc. The polynucleotide can be labeled or unlabeled, with radioactive or non-radioactive labels as known in the art. Kits can comprise one or more pairs of polynucleotides for amplifying nucleic acids specific for tissue selective genes, e.g., comprising a forward and reverse primer effective in PCR. These include both sense and anti-sense orientations. For instance, in PCR-based methods (such as RT-PCR), a pair of primers are typically used, one having a sense sequence and the other having an antisense sequence.

Another aspect of the present invention is a nucleotide sequence that is specific to, or for, a selective polynucleotide. The phrases "specific for" or "specific to" a polynucleotide have a functional meaning that the polynucleotide can be used to identify the presence of one or more target genes in a sample and distinguish them from non-target genes. It is specific in the sense that it can be used to detect polynucleotides above background noise ("non-specific binding"). A specific sequence is a defined order of nucleotides (or amino acid sequences, if it is a polypeptide sequence) which occurs in the polynucleotide, e.g., in the nucleotide sequences of the present invention, and which is characteristic of that target sequence, and substantially no non-target sequences. A probe or mixture of probes can comprise a sequence or sequences that are specific to a plurality of target sequences, e.g., where the sequence is a consensus sequence, a functional domain, etc., e.g., capable of recognizing a family of related genes. Such sequences can be used as probes in any of the methods described herein or incorporated by reference. Both sense and antisense nucleotide sequences are included. A specific polynucleotide according to the present invention can be determined routinely.

A polynucleotide comprising a specific sequence can be used as a hybridization probe to identify the presence of, e.g., human or mouse polynucleotide, in a sample comprising a mixture of polynucleotides, e.g., on a Northern blot. Hybridization can be performed under high stringent conditions (see, above) to select polynucleotides (and their complements which

can contain the coding sequence) having at least 90%, 95%, 99%, etc., identity (i.e., complementarity) to the probe, but less stringent conditions can also be used. A specific polynucleotide sequence can also be fused in-frame, at either its 5' or 3' end, to various nucleotide sequences as mentioned throughout the patent, including coding sequences for enzymes, detectable markers, GFP, etc, expression control sequences, etc.

A polynucleotide probe, especially one that is specific to a polynucleotide of the present invention, can be used in gene detection and hybridization methods as already described. In one embodiment, a specific polynucleotide probe can be used to detect whether a particular tissue or cell-type is present in a target sample. To carry out such a method, a selective polynucleotide can be chosen which is characteristic of the desired target tissue. Such polynucleotide is preferably chosen so that it is expressed or displayed in the target tissue, but not in other tissues which are present in the sample. For instance, if detection of pancreas, or kidney, it may not matter whether the selective polynucleotide is expressed in other tissues, as long as it is not expressed in cells normally present in blood, e.g., peripheral blood mononuclear cells. Starting from the selective polynucleotide, a specific polynucleotide probe can be designed which hybridizes (if hybridization is the basis of the assay) under the hybridization conditions to the selective polynucleotide, whereby the presence of the selective polynucleotide can be determined.

Probes which are specific for polynucleotides of the present invention can also be prepared using involve transcription-based systems, e.g., incorporating an RNA polymerase promoter into a selective polynucleotide of the present invention, and then transcribing anti-sense RNA using the polynucleotide as a template. See, e.g., U.S. Pat. No. 5,545,522.

Polynucleotide composition

A polynucleotide according to the present invention can comprise, e.g., DNA, RNA, synthetic polynucleotide, peptide polynucleotide, modified nucleotides, dsDNA, ssDNA, ssRNA, dsRNA, and mixtures thereof. A polynucleotide can be single- or double-stranded, triplex, DNA:RNA, duplexes, comprise hairpins, and other secondary structures, etc. Nucleotides comprising a polynucleotide can be joined via various known linkages, e.g., ester, sulfamate, sulfamide, phosphorothioate, phosphoramidate, methylphosphonate, carbamate, etc., depending on the desired purpose, e.g., resistance to nucleases, such as

RNAse H, improved in vivo stability, etc. See, e.g., U.S. Pat. No. 5,378,825. Any desired nucleotide or nucleotide analog can be incorporated, e.g., 6-mercaptopguanine, 8-oxo-guanine, etc.

Various modifications can be made to the polynucleotides, such as attaching
5 detectable markers (avidin, biotin, radioactive elements, fluorescent tags and dyes, energy transfer labels, energy-emitting labels, binding partners, etc.) or moieties which improve hybridization, detection, and/or stability. The polynucleotides can also be attached to solid supports, e.g., nitrocellulose, magnetic or paramagnetic microspheres (e.g., as described in U.S. Pat. No. 5,411,863; U.S. Pat. No. 5,543,289; for instance, comprising ferromagnetic,
10 supermagnetic, paramagnetic, superparamagnetic, iron oxide and polysaccharide), nylon, agarose, diazotized cellulose, latex solid microspheres, polyacrylamides, etc., according to a desired method. See, e.g., U.S. Pat. Nos. 5,470,967, 5,476,925, and 5,478,893.

Polynucleotide according to the present invention can be labeled according to any desired method. The polynucleotide can be labeled using radioactive tracers such as ³²P, ³⁵S,
15 ³H, or ¹⁴C, to mention some commonly used tracers. The radioactive labeling can be carried out according to any method, such as, for example, terminal labeling at the 3' or 5' end using a radiolabeled nucleotide, polynucleotide kinase (with or without dephosphorylation with a phosphatase) or a ligase (depending on the end to be labeled). A non-radioactive labeling can also be used, combining a polynucleotide of the present invention with residues having
20 immunological properties (antigens, haptens), a specific affinity for certain reagents (ligands), properties enabling detectable enzyme reactions to be completed (enzymes or coenzymes, enzyme substrates, or other substances involved in an enzymatic reaction), or characteristic physical properties, such as fluorescence or the emission or absorption of light at a desired wavelength, etc.

25 Nucleic acid detection methods

Another aspect of the present invention relates to methods and processes for detecting tissue selective genes. Detection methods have a variety of applications, including for diagnostic, prognostic, forensic, and research applications. To accomplish gene detection, a
30 polynucleotide in accordance with the present invention can be used as a "probe." The term "probe" or "polynucleotide probe" has its customary meaning in the art, e.g., a polynucleotide

which is effective to identify (e.g., by hybridization), when used in an appropriate process, the presence of a target polynucleotide to which it is designed. Identification can involve simply determining presence or absence, or it can be quantitative, e.g., in assessing amounts of a gene or gene transcript present in a sample. Probes can be useful in a variety of ways, such as for diagnostic purposes, to identify homologs, and to detect, quantitate, or isolate a polynucleotide of the present invention in a test sample.

Assays can be utilized which permit quantification and/or presence/absence detection of a target nucleic acid in a sample. Assays can be performed at the single-cell level, or in a sample comprising many cells, where the assay is "averaging" expression over the entire collection of cells and tissue present in the sample. Any suitable assay format can be used, including, but not limited to, e.g., Southern blot analysis, Northern blot analysis, polymerase chain reaction ("PCR") (e.g., Saiki et al., *Science*, 241:53, 1988; U.S. Pat. Nos. 4,683,195, 4,683,202, and 6,040,166; *PCR Protocols: A Guide to Methods and Applications*, Innis et al., eds., Academic Press, New York, 1990), reverse transcriptase polymerase chain reaction ("RT-PCR"), anchored PCR, rapid amplification of cDNA ends ("RACE") (e.g., Schaefer in *Gene Cloning and Analysis: Current Innovations*, Pages 99-115, 1997), ligase chain reaction ("LCR") (EP 320 308), one-sided PCR (Ohara et al., *Proc. Natl. Acad. Sci.*, 86:5673-5677, 1989), indexing methods (e.g., U.S. Pat. No. 5,508,169), *in situ* hybridization, differential display (e.g., Liang et al., *Nucl. Acid. Res.*, 21:3269-3275, 1993; U.S. Pat. Nos. 5,262,311, 5,599,672 and 5,965,409; WO97/18454; Prashar and Weissman, *Proc. Natl. Acad. Sci.*, 93:659-663, and U.S. Pat. Nos. 6,010,850 and 5,712,126; Welsh et al., *Nucleic Acid Res.*, 20:4965-4970, 1992, and U.S. Pat. No. 5,487,985) and other RNA fingerprinting techniques, nucleic acid sequence based amplification ("NASBA") and other transcription based amplification systems (e.g., U.S. Pat. Nos. 5,409,818 and 5,554,527; WO 88/10315), polynucleotide arrays (e.g., U.S. Pat. Nos. 5,143,854, 5,424,186; 5,700,637, 5,874,219, and 6,054,270; PCT WO 92/10092; PCT WO 90/15070), Qbeta Replicase (PCT/US87/00880), Strand Displacement Amplification ("SDA"), Repair Chain Reaction ("RCR"), nuclease protection assays, subtraction-based methods, Rapid-Scan™, etc. Additional useful methods include, but are not limited to, e.g., template-based amplification methods, competitive PCR (e.g., U.S. Pat. No. 5,747,251), redox-based assays (e.g., U.S. Pat. No. 5,871,918), Taqman-based assays (e.g., Holland et al., *Proc. Natl. Acad. Sci.*, 88:7276-7280, 1991; U.S. Pat. Nos.

5,210,015 and 5,994,063), real-time fluorescence-based monitoring (e.g., U.S. Pat. 5,928,907), molecular energy transfer labels (e.g., U.S. Pat. Nos. 5,348,853, 5,532,129, 5,565,322, 6,030,787, and 6,117,635; Tyagi and Kramer, *Nature Biotech.*, 14:303-309, 1996). Any method suitable for single cell analysis of gene or protein expression can be used, including in situ hybridization, immunocytochemistry, MACS, FACS, flow cytometry, etc. For single cell assays, expression products can be measured using antibodies, PCR, or other types of nucleic acid amplification (e.g., Brady et al., *Methods Mol. & Cell. Biol.* 2, 17-25, 1990; Eberwine et al., 1992, *Proc. Natl. Acad. Sci.*, 89, 3010-3014, 1992; U.S. Pat. No. 5,723,290). These and other methods can be carried out conventionally, e.g., as described in the mentioned publications.

Many of such methods may require that the polynucleotide is labeled, or comprises a particular nucleotide type useful for detection. The present invention includes such modified polynucleotides that are necessary to carry out such methods. Thus, polynucleotides can be DNA, RNA, DNA:RNA hybrids, PNA, etc., and can comprise any modification or substituent which is effective to achieve detection.

Detection can be desirable for a variety of different purposes, including research, diagnostic, prognostic, and forensic. For diagnostic purposes, it may be desirable to identify the presence or quantity of a polynucleotide sequence in a sample, where the sample is obtained from tissue, cells, body fluids, etc. In a preferred method as described in more detail below, the present invention relates to a method of detecting a polynucleotide comprising, contacting a target polynucleotide in a test sample with a polynucleotide probe under conditions effective to achieve hybridization between the target and probe; and detecting hybridization.

Any test sample in which it is desired to identify a polynucleotide or polypeptide thereof can be used, including, e.g., blood, urine, saliva, stool (for extracting nucleic acid, see, e.g., U.S. Pat. No. 6,177,251), swabs comprising tissue, biopsied tissue, tissue sections, cultured cells, etc.

Detection can be accomplished in combination with polynucleotide probes for other genes, e.g., genes which are expressed in other disease states, tissues, cells, such as brain, heart, kidney, spleen, thymus, liver, stomach, small intestine, colon, muscle, lung, testis, placenta, pituitary, thyroid, skin, adrenal gland, pancreas, salivary gland, uterus, ovary,

prostate gland, peripheral blood cells (T-cells, lymphocytes, etc.), embryo, breast, fat, adult and embryonic stem cells, etc.

Polynucleotides can be used in wide range of methods and compositions, including for detecting, diagnosing, staging, grading, assessing, prognosticating, etc. diseases and disorders associated with tissue selective genes, for monitoring or assessing therapeutic and/or preventative measures, in ordered arrays, etc. Any method of detecting genes and polynucleotides can be used; certainly, the present invention is not to be limited how such methods are implemented.

Along these lines, the present invention relates to methods of detecting polynucleotides of the present invention in a sample comprising nucleic acid. Such methods can comprise one or more the following steps in any effective order, e.g., contacting said sample with a polynucleotide probe under conditions effective for said probe to hybridize specifically to nucleic acid in said sample, and detecting the presence or absence of probe hybridized to nucleic acid in said sample, wherein said probe is a polynucleotide which is described herein, a polynucleotide having, e.g., about 70%, 80%, 85%, 90%, 95%, 99%, or more sequence identity thereto, effective or specific fragments thereof, or complements thereto. The detection method can be applied to any sample, e.g., cultured primary, secondary, or established cell lines, tissue biopsy, blood, urine, stool, cerebral spinal fluid, and other bodily fluids, for any purpose.

Contacting the sample with probe can be carried out by any effective means in any effective environment. It can be accomplished in a solid, liquid, frozen, gaseous, amorphous, solidified, coagulated, colloid, etc., mixtures thereof, matrix. For instance, a probe in an aqueous medium can be contacted with a sample which is also in an aqueous medium, or which is affixed to a solid matrix, or vice-versa.

Generally, as used throughout the specification, the term "effective conditions" means, e.g., the particular milieu in which the desired effect is achieved. Such a milieu, includes, e.g., appropriate buffers, oxidizing agents, reducing agents, pH, co-factors, temperature, ion concentrations, suitable age and/or stage of cell (such as, in particular part of the cell cycle, or at a particular stage where particular genes are being expressed) where cells are being used, culture conditions (including substrate, oxygen, carbon dioxide, etc.). When hybridization is the chosen means of achieving detection, the probe and sample can be

combined such that the resulting conditions are functional for said probe to hybridize specifically to nucleic acid in said sample.

The phrase "hybridize specifically" indicates that the hybridization between single-stranded polynucleotides is based on nucleotide sequence complementarity. The effective
5 conditions are selected such that the probe hybridizes to a preselected and/or definite target nucleic acid in the sample. For instance, if detection of a polynucleotide set forth herein is desired, a probe can be selected which can hybridize to such target gene under high stringent conditions, without significant hybridization to other genes in the sample. To detect
10 homologs of a polynucleotide set forth in herein, the effective hybridization conditions can be less stringent, and/or the probe can comprise codon degeneracy, such that a homolog is detected in the sample.

As already mentioned, the methods can be carried out by any effective process, e.g., by Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, *in situ* hybridization, etc., as indicated above. When PCR based techniques are
15 used, two or more probes are generally used. One probe can be specific for a defined sequence which is characteristic of a selective polynucleotide, but the other probe can be specific for the selective polynucleotide, or specific for a more general sequence, e.g., a sequence such as polyA which is characteristic of mRNA, a sequence which is specific for a promoter, ribosome binding site, or other transcriptional features, a consensus sequence (e.g.,
20 representing a functional domain). For the former aspects, 5' and 3' probes (e.g., polyA, Kozak, etc.) are preferred which are capable of specifically hybridizing to the ends of transcripts. When PCR is utilized, the probes can also be referred to as "primers" in that they can prime a DNA polymerase reaction.

In addition to testing for the presence or absence of polynucleotides, the present
25 invention also relates to determining the amounts at which polynucleotides of the present invention are expressed in sample and determining the differential expression of such polynucleotides in samples. Such methods can involve substantially the same steps as described above for presence/absence detection, e.g., contacting with probe, hybridizing, and detecting hybridized probe, but using more quantitative methods and/or comparisons to
30 standards.

The amount of hybridization between the probe and target can be determined by any suitable methods, e.g., PCR, RT-PCR, RACE PCR, Northern blot, polynucleotide microarrays, Rapid-Scan, etc., and includes both quantitative and qualitative measurements. For further details, see the hybridization methods described above and below. Determining

5 by such hybridization whether the target is differentially expressed (e.g., up-regulated or down-regulated) in the sample can also be accomplished by any effective means. For instance, the target's expression pattern in the sample can be compared to its pattern in a known standard, such as in a normal tissue, or it can be compared to another gene in the same sample. When a second sample is utilized for the comparison, it can be a sample of normal
10 tissue that is known not to contain diseased cells. The comparison can be performed on samples which contain the same amount of RNA (such as polyadenylated RNA or total RNA), or, on RNA extracted from the same amounts of starting tissue. Such a second sample can also be referred to as a control or standard. Hybridization can also be compared to a second target in the same tissue sample. Experiments can be performed that determine a
15 ratio between the target nucleic acid and a second nucleic acid (a standard or control), e.g., in a normal tissue. When the ratio between the target and control are substantially the same in a normal and sample, the sample is determined or diagnosed not to contain cells. However, if the ratio is different between the normal and sample tissues, the sample is determined to contain, e.g., kidney, pancreas, or immune cells. The approaches can be combined, and one
20 or more second samples, or second targets can be used. Any second target nucleic acid can be used as a comparison, including "housekeeping" genes, such as beta-actin, alcohol dehydrogenase, or any other gene whose expression does not vary depending upon the disease status of the cell.

25 Methods of identifying polymorphisms, mutations, etc.

Polynucleotides of the present invention can also be utilized to identify mutant alleles, SNPs, gene rearrangements and modifications, and other polymorphisms of the wild-type gene. Mutant alleles, polymorphisms, SNPs, etc., can be identified and isolated from subjects with diseases that are known, or suspected to have, a genetic component.

30 Identification of such genes can be carried out routinely (see, above for more guidance), e.g., using PCR, hybridization techniques, direct sequencing, mismatch reactions (see, e.g.,

above), RFLP analysis, SSCP (e.g., Orita et al., *Proc. Natl. Acad. Sci.*, 86:2766, 1992), etc., where a polynucleotide having a sequence selected from the polynucleotides of the present invention is used as a probe. The selected mutant alleles, SNPs, polymorphisms, etc., can be used diagnostically to determine whether a subject has, or is susceptible to a disorder

- 5 associated with tissue selective genes disclosed herein, as well as to design therapies and predict the outcome of the disorder. Methods involve, e.g., diagnosing a disorder or determining susceptibility to a disorder, comprising, detecting the presence of a mutation in a gene represented by a polynucleotide selected from the sequences disclosed herein. The detecting can be carried out by any effective method, e.g., obtaining cells from a subject,
- 10 determining the gene sequence or structure of a target gene (using, e.g., mRNA, cDNA, genomic DNA, etc), comparing the sequence or structure of the target gene to the structure of the normal gene, whereby a difference in sequence or structure indicates a mutation in the gene in the subject. Polynucleotides can also be used to test for mutations, SNPs, polymorphisms, etc., e.g., using mismatch DNA repair technology as described in U.S. Pat. No. 5,683,877; U.S. Pat. No. 5,656,430; Wu et al., *Proc. Natl. Acad. Sci.*, 89:8779-8783,
- 15 1992.

The present invention also relates to methods of detecting polymorphisms in tissue selective genes, comprising, e.g., comparing the structure of: genomic DNA comprising all or part of a tissue selective gene, mRNA comprising all or part of a tissue selective gene, cDNA

20 comprising all or part of a tissue selective gene, or a polypeptide comprising all or part of a tissue selective gene, with the structure the polynucleotides set forth herein. The methods can be carried out on a sample from any source, e.g., cells, tissues, body fluids, blood, urine, stool, hair, egg, sperm, cerebral spinal fluid, biopsy samples, serum, etc.

- These methods can be implemented in many different ways. For example,
- 25 "comparing the structure" steps include, but are not limited to, comparing restriction maps, nucleotide sequences, amino acid sequences, RFLPs, Dnase sites, DNA methylation fingerprints (e.g., U.S. Pat. No. 6,214,556), protein cleavage sites, molecular weights, electrophoretic mobilities, charges, ion mobility, etc., between standard and a test genes. The term "structure" can refer to any physical characteristics or configurations which can be used
- 30 to distinguish between nucleic acids and polypeptides. The methods and instruments used to accomplish the comparing step depends upon the physical characteristics which are to be

compared. Thus, various techniques are contemplated, including, e.g., sequencing machines (both amino acid and polynucleotide), electrophoresis, mass spectrometer (U.S. Pat. Nos. 6,093,541, 6,002,127), liquid chromatography, HPLC, etc.

To carry out such methods, "all or part" of the gene or polypeptide can be compared.

- 5 For example, if nucleotide sequencing is utilized, the entire gene can be sequenced, including promoter, introns, and exons, or only parts of it can be sequenced and compared, e.g., exon 1, exon 2, etc.

Mutagenesis

- 10 Mutated polynucleotide sequences of the present invention are useful for various purposes, e.g., to create mutations of the polypeptides they encode, to identify functional regions of genomic DNA, to produce probes for screening libraries, etc. Mutagenesis can be carried out routinely according to any effective method, e.g., oligonucleotide-directed (Smith, M., *Ann. Rev. Genet.* 19:423-463, 1985), degenerate oligonucleotide-directed (Hill et al.,
15 *Method Enzymology*, 155:558-568, 1987), region-specific (Myers et al., *Science*, 229:242-246, 1985; Derbyshire et al., *Gene*, 46:145, 1986; Ner et al., *DNA*, 7:127, 1988), linker-scanning (McKnight and Kingsbury, *Science*, 217:316-324, 1982), directed using PCR, recursive ensemble mutagenesis (Arkin and Yourvan, *Proc. Natl. Acad. Sci.*, 89:7811-7815, 1992), random mutagenesis (e.g., U.S. Pat. Nos. 5,096,815; 5,198,346; and 5,223,409), site-
20 directed mutagenesis (e.g., Walder et al., *Gene*, 42:133, 1986; Bauer et al., *Gene*, 37:73, 1985; Craik, *Bio Techniques*, January 1985, 12-19; Smith et al., *Genetic Engineering: Principles and Methods*, Plenum Press, 1981), phage display (e.g., Lowman et al., *Biochem.* 30:10832-10837, 1991; Ladner et al., U.S. Pat. No. 5,223,409; Huse, WIPO Publication WO 92/06204), etc. Desired sequences can also be produced by the assembly of target sequences
25 using mutually priming oligonucleotides (Uhlmann, *Gene*, 71:29-40, 1988). For directed mutagenesis methods, analysis of the three-dimensional structure of the polypeptide can be used to guide and facilitate making mutants which effect polypeptide activity. Sites of substrate-enzyme interaction or other biological activities can also be determined by analysis of crystal structure as determined by such techniques as nuclear magnetic resonance,
30 crystallography or photoaffinity labeling. See, for example, de Vos et al., *Science* 255:306-312, 1992; Smith et al., *J. Mol. Biol.* 224:899-904, 1992; Wlodaver et al., *FEBS Lett.*

309:59-64, 1992.

In addition, libraries of genes and fragments thereof can be used for screening and selection of genes variants. For instance, a library of coding sequences can be generated by treating a double-stranded DNA with a nuclease under conditions where the nicking occurs, e.g., only once per molecule, denaturing the double-stranded DNA, renaturing it to for
5 double-stranded DNA that can include sense/antisense pairs from different nicked products, removing single-stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting DNAs into an expression vector. By this method, expression libraries can be made comprising "mutagenized" tissue selective genes. The entire coding
10 sequence or parts thereof can be used.

Polynucleotide expression, polypeptides produced thereby, and specific-binding partners thereto.

A polynucleotide according to the present invention can be expressed in a variety of
15 different systems, in vitro and in vivo, according to the desired purpose. For example, a polynucleotide can be inserted into an expression vector, introduced into a desired host, and cultured under conditions effective to achieve expression of a polypeptide coded for by the polynucleotide, to search for specific binding partners. Effective conditions include any culture conditions which are suitable for achieving production of the polypeptide by the host
20 cell, including effective temperatures, pH, medium, additives to the media in which the host cell is cultured (e.g., additives which amplify or induce expression such as butyrate, or methotrexate if the coding polynucleotide is adjacent to a dhfr gene), cycloheximide, cell densities, culture dishes, etc. A polynucleotide can be introduced into the cell by any effective method including, e.g., naked DNA, calcium phosphate precipitation,
25 electroporation, injection, DEAE-Dextran mediated transfection, fusion with liposomes, association with agents which enhance its uptake into cells, viral transfection. A cell into which a polynucleotide of the present invention has been introduced is a transformed host cell. The polynucleotide can be extrachromosomal or integrated into a chromosome(s) of the host cell. It can be stable or transient. An expression vector is selected for its compatibility
30 with the host cell. Host cells include, mammalian cells, e.g., COS, CV1, BHK, CHO, HeLa, LTK, NIH 3T3, insect cells, such as Sf9 (*S. frugipeda*) and *Drosophila*, bacteria, such as *E.*

coli, Streptococcus, bacillus, yeast, such as *Sacharomyces*, *S. cerevisiae*, fungal cells, plant cells, embryonic or adult stem cells (e.g., mammalian, such as mouse or human),

immune system cell lines, HH (ATCC CRL 2105), MOLT-4 (ATCC CRL 1582), MJ (ATCC CRL-8294), SK7 (ATCC HB-8584), SK8 (ATCC HB-8585), HM1 (HB-8586), H9

5 (ATCC HTB-176), HuT 78 (ATCC TIB-161), HuT 102 (ATCC TIB-162), Jurkat,

B-cell lines, B-cell precursor lines, NALM-36, B-cell and other lymphocyte lines: immortalized with Epstein-Barr virus (transformed B lymphoblastoid), stromal cell lines, myelomas, HBM-Noda, WEHI231,

10 reticuloendothelial cells, endothelial cells, white blood cells, macrophages, antigen-presenting cells, lymphocytes, GDM-1 (ATCC CRL-2627), THP-1 (ATCC TIB-202), HL-60 (ATCC CCL-240), and derivatives thereof, including primary and established cell lines thereof,

kidney cell lines, 293, G-402 (ATCC CRL-1440), ACHN (ATCC CRL-1611), Vero (ATCC CCL-81), 786-O (ATCC CRL-1932), 769-P (ATCC CRL-1933), CCD 1103 KIDTr (ATCC CRL-2304), CCD 1105 KIDTr (ATCC CRL-2305), Hs 835.T (ATCC CRL-7569),
15 Hs 926.T (ATCC CRL-7678), Caki-1 (ATCC HTB-46), Caki-2 (ATCC HTB-47), SW 839 (ATCC HTB-49), LLC-MK2 (ATCC CCL-7), BHK-21 (ATCC CCL-10), MDCK, CV-1, (ATCC CRL-1573), KNRK (ATCC CRL-1569), NRK-49F (ATCC CRL-1570), A-704 (ATCC HTB-45), etc., established and primary kidney cells,

20 pancreas cell lines, , insulinoma cell lines, INS-H1, MIN6N8, RIN 1046-38, RIN-5AH, RIN-A12, RINm5F, capan-1, capan-2, MIA PaCa-2 (ATCC CRL-1420), PANC-1 (ATCC CRL-1469), AsPC-1 (ATCC CRL-1682), SU-86.86 (ATCC CRL-1837), CFPAC-1 (ATCC CRL-1918), HPAF-II (ATCC CRL-1937), TGP61 (ATCC CRL-2135) and other TGP lines, SW 1990 (ATCC CRL-2172), Mpanc-96 (ATCC CRL-2380), MS1 VEGF
25 (ATCC CRL-2460), Beta-TC-6 (ATCC CRL-11506), LTPA (ATCC CRL-2389), 266-6 (ATCC CRL-2151), MS1 (ATCC CRL-2779), SVR (ATCC CRL-2280), NIT-2 (ATCC CRL-2364), alphaTC1 Clone 9 (ATCC CRL-2350), ATCC CRL-1492, BxPC-3 (ATCC CRL-1687), HPAC (ATCC CRL-2119), U.S. Pat. Nos. 6,110,743, 5,928,942, 5,888,816, 5,888,705, and 5,723,333, etc., established and primary pancreas cells (e.g., according to
30 Hellerstrom et al., *Diabetes*, 28:769-76, 1979),

retinal cell lines, RF/6A (CRL 1780), ARPE-19 (CRL-2302), ARPE-19/HPV-16 (CRL-2502), Y79 (HTB-18), WERI-Rb-1 (HTB-169), RPE-J (CRL-2240), SO-Rb50 (retinoblastoma cell line), RBL, HER-Xho1-CC2, WERI-Rb24 (Sery et al., *J. Pediatr. Ophthalmol. Strabismus*, 4:212-217, 1990), WERI-Rb27 (Sery et al., *J. Pediatr. Ophthalmol. Strabismus*, 4:212-217, 1990), HXO-Rb44, fetal retina cells, retinoblastoma cells, choroidal endothelial cells (e.g., Chor 55), etc., established and primary retinal cells (For other cell lines and methods thereof, see, also, Griege et al, *Differentiation*, 45:250-7, 1990; Bernstein et al., *Invest. Ophthalmol. Vis. Sci.*, 35:3931-3937, 1994; Howes et al., *Invest. Ophthalmol. Vis. Sci.*, 35:342-351, 1994).

10 Expression control sequences are similarly selected for host compatibility and a desired purpose, e.g., high copy number, high amounts, induction, amplification, controlled expression. Other sequences which can be employed include enhancers such as from SV40, CMV, RSV, inducible promoters, cell-type specific elements, or sequences which allow selective or specific cell expression. Promoters that can be used to drive its expression, include, e.g., the endogenous promoter, MMTV, SV40, trp, lac, tac, or T7 promoters for
15 bacterial hosts; or alpha factor, alcohol oxidase, or PGH promoters for yeast. RNA promoters can be used to produced RNA transcripts, such as T7 or SP6. See, e.g., Melton et al., *Polynucleotide Res.*, 12(18):7035-7056, 1984; Dunn and Studier. *J. Mol. Bio.*, 166:477-435, 1984; U.S. Pat. No. 5,891,636; Studier et al., *Gene Expression Technology, Methods in*
20 *Enzymology*, 85:60-89, 1987. In addition, as discussed above, translational signals (including in-frame insertions) can be included.

When a polynucleotide is expressed as a heterologous gene in a transfected cell line, the gene is introduced into a cell as described above, under effective conditions in which the gene is expressed. The term "heterologous" means that the gene has been introduced into the
25 cell line by the "hand-of-man." Introduction of a gene into a cell line is discussed above. The transfected (or transformed) cell expressing the gene can be lysed or the cell line can be used intact.

For expression and other purposes, a polynucleotide can contain codons found in a naturally-occurring gene, transcript, or cDNA, for example, e.g., as set forth in herein or it
30 can contain degenerate codons coding for the same amino acid sequences. For instance,

it may be desirable to change the codons in the sequence to optimize the sequence for expression in a desired host. See, e.g., U.S. Pat. Nos. 5,567,600 and 5,567,862.

A polypeptide according to the present invention can be recovered from natural sources, transformed host cells (culture medium or cells) according to the usual methods, including, detergent extraction (e.g., non-ionic detergent, Triton X-100, CHAPS, octylglucoside, Igepal CA-630), ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxyapatite chromatography, lectin chromatography, gel electrophoresis. Protein refolding steps can be used, as necessary, in completing the configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for purification steps. Another approach is express the polypeptide recombinantly with an affinity tag (Flag epitope, HA epitope, myc epitope, 6xHis, maltose binding protein, chitinase, etc) and then purify by anti-tag antibody-conjugated affinity chromatography.

The present invention also relates to specific-binding partners. These include antibodies which are specific for polypeptides encoded by polynucleotides of the present invention, as well as other binding-partners which interact with polynucleotides and polypeptides of the present invention. Protein-protein interactions between polypeptides and binding partners can be identified using any suitable methods, e.g., protein binding assays (e.g., filtration assays, chromatography, etc.), yeast two-hybrid system (Fields and Song, *Nature*, 340: 245-247, 1989), protein arrays, gel-shift assays, FRET (fluorescence resonance energy transfer) assays, etc. Nucleic acid interactions (e.g., protein-DNA or protein-RNA) can be assessed using gel-shift assays, e.g., as carried out in U.S. Pat. No. 6,333,407 and 5,789,538.

Antibodies, e.g., polyclonal, monoclonal, recombinant, chimeric, humanized, single-chain, Fab, and fragments thereof, can be prepared according to any desired method. Antibodies, and immune responses, can also be generated by administering naked DNA See, e.g., U.S. Pat. Nos. 5,703,055; 5,589,466; 5,580,859. Antibodies can be used from any source, including, goat, rabbit, mouse, chicken (e.g., IgY; see, Duan, WO/029444 for methods of making antibodies in avian hosts, and harvesting the antibodies from the eggs). An antibody specific for a polypeptide means that the antibody recognizes a defined sequence of

amino acids within or including the polypeptide. Other specific binding partners include, e.g., aptamers and PNA. Antibodies can be prepared against specific epitopes or domains.

Antibodies can also be humanized, e.g., where they are to be used therapeutically. Methods for obtaining human antibodies, e.g., from transgenic mice are described, e.g., in Green et al., *Nature Genet.* 7:13 (1994); Lonberg et al., *Nature* 368:856 (1994); and Taylor et al., *Int. Immunol.* 6:579 (1994). Antibody fragments of the present invention can be prepared by any suitable method, Fab and Fc fragments. single-chain antibodies can also be used. Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest.

The term "antibody" as used herein includes intact molecules as well as fragments thereof, such as Fab, F(ab')₂, and Fv which are capable of binding to an epitopic determinant present in Bin1 polypeptide. Such antibody fragments retain some ability to selectively bind with its antigen or receptor. The term "epitope" refers to an antigenic determinant on an antigen to which the paratope of an antibody binds. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Antibodies can be prepared against specific epitopes or polypeptide domains.

Antibodies which bind to polypeptides of the present invention can be prepared using an intact polypeptide or fragments containing small peptides of interest as the immunizing antigen. For example, it may be desirable to produce antibodies that specifically bind to the N- or C-terminal domains of the tissue selective polypeptides of the present invention. The polypeptide or peptide used to immunize an animal which is derived from translated cDNA or chemically synthesized which can be conjugated to a carrier protein, if desired. Such commonly used carriers which are chemically coupled to the immunizing peptide include keyhole limpet hemocyanin (KLH), thyroglobulin, bovine serum albumin (BSA), and tetanus toxoid.

Methods of detecting polypeptides

Polypeptides coded for by genes of the present invention can be detected, visualized, determined, quantitated, etc. according to any effective method. useful methods include, e.g., but are not limited to, immunoassays, RIA (radioimmunassay), ELISA, (enzyme-linked-immunosorbent assay), immunofluorescence, flow cytometry, histology, electron microscopy,
5 light microscopy, in situ assays, immunoprecipitation, Western blot, etc.

Immunoassays may be carried in liquid or on biological support. For instance, a sample (e.g., blood, serum, stool, urine, cells, tissue, cerebral spinal fluid, body fluids, etc.) can be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support that is capable of immobilizing cells, cell particles or
10 soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled specific antibody. The solid phase support can then be washed with a buffer a second time to remove unbound antibody. The amount of bound label on solid support may then be detected by conventional means.

A "solid phase support or carrier" includes any support capable of binding an antigen,
15 antibody, or other specific binding partner. Supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, and magnetite. A support material can have any structural or physical configuration. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the
20 surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads

One of the many ways in which gene peptide-specific antibody can be detectably labeled is by linking it to an enzyme and using it in an enzyme immunoassay (EIA). See, e.g., Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)," 1978, Diagnostic
25 Horizons 2, 1-7, Microbiological Associates Quarterly Publication, Walkersville, Md.); Voller, A. et al., 1978, J. Clin. Pathol. 31, 507-520; Butler, J. E., 1981, Meth. Enzymol. 73, 482-523; Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, Fla.. The enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety that can be
30 detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes that can be used to detectably label the antibody include, but are not limited to, malate

dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, .alpha.-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, .beta.-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase,

- 5 glucoamylase and acetylcholinesterase. The detection can be accomplished by colorimetric methods that employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

Detection may also be accomplished using any of a variety of other immunoassays.

- 10 For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect peptides through the use of a radioimmunoassay (RIA). See, e.g., Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986. The radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography.

- 15 It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine. The antibody can also be detectably
20 labeled using fluorescence emitting metals such as those in the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

- The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by
25 detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

- Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological
30 systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of

luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Diagnostic

5 The present invention also relates to methods and compositions for diagnosing a disorder, or determining susceptibility to a disorder, using polynucleotides, polypeptides, and specific-binding partners of the present invention to detect, assess, determine, etc., a tissue selective gene. In such methods, the gene can serve as a marker for the disorder, e.g., where the gene, when mutant, is a direct cause of the disorder; where the gene is affected by another
10 gene(s) which is directly responsible for the disorder, e.g., when the gene is part of the same signaling pathway as the directly responsible gene; and, where the gene is chromosomally linked to the gene(s) directly responsible for the disorder, and segregates with it. Many other situations are possible. To detect, assess, determine, etc., a probe specific for the gene can be employed as described above and below. Any method of detecting and/or assessing the gene
15 can be used, including detecting expression of the gene using polynucleotides, antibodies, or other specific-binding partners.

 The phrase "diagnosing" indicates that it is determined whether the sample has the disorder. A "disorder" means, e.g., any abnormal condition as in a disease or malady. "Determining a subject's susceptibility to a disease or disorder" indicates that the subject is
20 assessed for whether s/he is predisposed to get such a disease or disorder, where the predisposition is indicated by abnormal expression of the gene (e.g., gene mutation, gene expression pattern is not normal, etc.). Predisposition or susceptibility to a disease may result when a such disease is influenced by epigenetic, environmental, etc., factors. Diagnosing includes prenatal screening where samples from the fetus or embryo (e.g., via amniocentesis
25 or CV sampling) are analyzed for the expression of the gene.

 By the phrase "assessing expression of a gene or polynucleotide," it is meant that the functional status of the gene is evaluated. This includes, but is not limited to, measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of
30 polypeptide coded for by said gene. Thus, the term "assessing expression" includes evaluating the all aspects of the transcriptional and translational machinery of the gene. For

instance, if a promoter defect causes, or is suspected of causing, the disorder, then a sample can be evaluated (i.e., "assessed") by looking (e.g., sequencing or restriction mapping) at the promoter sequence in the gene, by detecting transcription products (e.g., RNA), by detecting translation product (e.g., polypeptide). Any measure of whether the gene is functional can be used, including, polypeptide, polynucleotide, and functional assays for the gene's biological activity.

In making the assessment, it can be useful to compare the results to a normal gene, e.g., a gene which is not associated with the disorder. The nature of the comparison can be determined routinely, depending upon how the assessing is accomplished. If, for example, the mRNA levels of a sample is detected, then the mRNA levels of a normal can serve as a comparison, or a gene which is known not to be affected by the disorder. Methods of detecting mRNA are well known, and discussed above, e.g., but not limited to, Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, etc. Similarly, if polypeptide production is used to evaluate the gene, then the polypeptide in a normal tissue sample can be used as a comparison, or, polypeptide from a different gene whose expression is known not to be affected by the disorder. These are only examples of how such a method could be carried out.

The genes and polypeptides of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions as mentioned above. The present invention relates to methods of identifying a genetic basis for a disease or disease-susceptibility, comprising, e.g., determining the association of a disease or disease-susceptibility with a gene of the present invention. An association between a disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target. Any region of the gene can be used as a source of the DNA marker, exons, introns, intergenic regions, etc.

Human linkage maps can be constructed to establish a relationship between a gene and a disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the

various individual molecular markers. Maps can be produced for an individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identify the gene responsible for the phenotype. See, e.g., Kruglyak et al., *Am. J. Hum. Genet.*, 58, 1347-1363, 1996; Matisse et al., *Nat. Genet.*, 6(4):384-90, 1994.

Assessing the effects of therapeutic and preventative interventions (e.g., administration of a drug, chemotherapy, radiation, etc.) on disorders is a major effort in drug discovery, clinical medicine, and pharmacogenomics. The evaluation of therapeutic and preventative measures, whether experimental or already in clinical use, has broad applicability, e.g., in clinical trials, for monitoring the status of a patient, for analyzing and assessing animal models, and in any scenario involving disease treatment and prevention. Analyzing the expression profiles of polynucleotides of the present invention can be utilized as a parameter by which interventions are judged and measured. Treatment of a disorder can change the expression profile in some manner which is prognostic or indicative of the drug's effect on it. Changes in the profile can indicate, e.g., drug toxicity, return to a normal level, etc. Accordingly, the present invention also relates to methods of monitoring or assessing a therapeutic or preventative measure (e.g., chemotherapy, radiation, anti-neoplastic drugs, antibodies, etc.) in a subject having a disorder, or, susceptible to such a disorder, comprising, e.g., detecting the expression levels of one or more tissue selective genes. A subject can be a cell-based assay system, non-human animal model, human patient, etc. Detecting can be accomplished as described for the methods above and below. By "therapeutic or preventative intervention," it is meant, e.g., a drug administered to a patient, surgery, radiation, chemotherapy, and other measures taken to prevent, treat, or diagnose a disorder.

The present invention also relates to methods of using binding partners, such as antibodies, to deliver active agents to the tissue (e.g., kidney or pancreas or an immune cells) for a variety of different purposes, including, e.g., for diagnostic, therapeutic, and research purposes. Methods can involve delivering or administering an active agent to the tissue, comprising, e.g., administering to a subject in need thereof, an effective amount of an active agent coupled to a binding partner specific for a tissue selective polypeptide, wherein said binding partner is effective to deliver said active agent specifically to the target tissue.

Any type of active agent can be used in combination with it, including, therapeutic, cytotoxic, cytostatic, chemotherapeutic, anti-neoplastic, anti-proliferative, anti-biotic, etc., agents. A chemotherapeutic agent can be, e.g., DNA-interactive agent, alkylating agent, antimetabolite, tubulin-interactive agent, hormonal agent, hydroxyurea, Cisplatin,

- 5 Cyclophosphamide, Altretamine, Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposide, paclitaxel, cytoxan, 2-methoxy-carbonyl-amino-benzimidazole, Plicamycin, Methotrexate, Fluorouracil, Fluorodeoxyuridin, CB3717, Azacitidine, Floxuridine, Mercaptopurine, 6-Thioguanine, Pentostatin, Cytarabine, Fludarabine, etc. Agents can also be contrast agents useful in imaging technology, e.g., X-ray, CT, CAT, MRI, ultrasound,
10 PET, SPECT, and scintographic.

- An active agent can be associated in any manner with a binding partner which is effective to achieve its delivery specifically to the target. Specific delivery or targeting indicates that the agent is provided to the tissue, without being substantially provided to other tissues. This is useful especially where an agent is toxic, and specific targeting to the tissue
15 enables the majority of the toxicity to be aimed at the tissue, with as small as possible effect on other tissues in the body. The association of the active agent and the binding partner ("coupling") can be direct, e.g., through chemical bonds between the binding partner and the agent, or, via a linking agent, or the association can be less direct, e.g., where the active agent is in a liposome, or other carrier, and the binding partner is associated with the liposome
20 surface. In such case, the binding partner can be oriented in such a way that it is able to bind to tissue selective polypeptide, e.g., exposed on the cell surface. Methods for delivery of DNA via a cell-surface receptor is described, e.g., in U.S. Pat. No. 6,339,139.

Identifying agent methods

- 25 The present invention also relates to methods of identifying agents, and the agents themselves, which modulate tissue selective genes. These agents can be used to modulate the biological activity of the polypeptide encoded for the gene, or the gene, itself. Agents which regulate the gene or its product are useful in variety of different environments, including as medicinal agents to treat or prevent disorders associated with genes and as research reagents
30 to modify the function of tissues and cell.

Methods of identifying agents generally comprise steps in which an agent is placed in contact with the gene, its transcription product, its translation product, or other target, and then a determination is performed to assess whether the agent "modulates" the target. The specific method utilized will depend upon a number of factors, including, e.g., the target (i.e.,
5 is it the gene or polypeptide encoded by it), the environment (e.g., in vitro or in vivo), the composition of the agent, etc.

For modulating the expression of tissue selective genes, a method can comprise, in any effective order, one or more of the following steps, e.g., contacting a gene (e.g., in a cell population) with a test agent under conditions effective for said test agent to modulate the
10 expression of tissue selective genes, and determining whether said test agent modulates said genes. An agent can modulate expression of a tissue selective gene at any level, including transcription (e.g., by modulating the promoter), translation, and/or perdurance of the nucleic acid (e.g., degradation, stability, etc.) in the cell.

For modulating the biological activity of polypeptides, a method can comprise, in any
15 effective order, one or more of the following steps, e.g., contacting a polypeptide (e.g., in a cell, lysate, or isolated) with a test agent under conditions effective for said test agent to modulate the biological activity of said polypeptide, and determining whether said test agent modulates said biological activity.

Contacting a gene or polypeptide with the test agent can be accomplished by any
20 suitable method and/or means that places the agent in a position to functionally control expression or biological activity. Functional control indicates that the agent can exert its physiological effect through whatever mechanism it works. The choice of the method and/or means can depend upon the nature of the agent and the condition and type of environment in which the gene or polypeptide is presented, e.g., lysate, isolated, or in a cell population (such
25 as, *in vivo*; *in vitro*, organ explants, etc.). For instance, if the cell population is an *in vitro* cell culture, the agent can be contacted with the cells by adding it directly into the culture medium. If the agent cannot dissolve readily in an aqueous medium, it can be incorporated into liposomes, or another lipophilic carrier, and then administered to the cell culture. Contact can also be facilitated by incorporation of agent with carriers and delivery molecules
30 and complexes, by injection, by infusion, etc.

Agents can be directed to, or targeted to, any part of the polypeptide which is

effective for modulating it. For example, agents, such as antibodies and small molecules, can be targeted to cell-surface, exposed, extracellular, ligand binding, functional, etc., domains of the polypeptide. Agents can also be directed to intracellular regions and domains, e.g., regions where the polypeptide couples or interacts with intracellular or intramembrane

5 binding partners.

After the agent has been administered in such a way that it can gain access, it can be determined whether the test agent modulates expression or biological activity. Modulation can be of any type, quality, or quantity, e.g., increase, facilitate, enhance, up-regulate, stimulate, activate, amplify, augment, induce, decrease, down-regulate, diminish, lessen, 10 reduce, etc. The modulatory quantity can also encompass any value, e.g., 1%, 5%, 10%, 50%, 75%, 1-fold, 2-fold, 5-fold, 10-fold, 100-fold, etc. To modulate expression means, e.g., that the test agent has an effect on its expression, e.g., to effect the amount of transcription, to effect RNA splicing, to effect translation of the RNA into polypeptide, to effect RNA or polypeptide stability, to effect polyadenylation or other processing of the RNA, to effect post- 15 transcriptional or post-translational processing, etc. To modulate biological activity means, e.g., that a functional activity of the polypeptide is changed in comparison to its normal activity in the absence of the agent. This effect includes, increase, decrease, block, inhibit, enhance, etc.

A test agent can be of any molecular composition, e.g., chemical compounds, 20 biomolecules, such as polypeptides, lipids, nucleic acids (e.g., antisense), carbohydrates, antibodies, ribozymes, double-stranded RNA, aptamers, etc. For example, if a polypeptide to be modulated is a cell-surface molecule, a test agent can be an antibody that specifically recognizes it and, e.g., causes the polypeptide to be internalized, leading to its down regulation on the surface of the cell. Such an effect does not have to be permanent, but can 25 require the presence of the antibody to continue the down-regulatory effect. Antibodies can also be used to modulate the biological activity of a polypeptide in a lysate or other cell-free form.

Additional cell-based test systems suitable for the analysis of GPCR polypeptides are summarized in Marchese et al. (1999, Trends in Pharmacol. Sci. 20: 370-375) and comprise 30 so-called "ligand screening assays." For example in yeast cells the pheromon receptor can be replaced by a GPCR according to the invention. The effect of test substances on the receptor

can be determined upon modulation of histidine synthesis, i.e. by growing in histidine-free medium. In addition using cells transfected with nucleic acids according to the invention it can be analyzed whether test substances mediate translocation of a detectable arrestins, for example of a arrestin-GFP-fusion protein. Moreover, it can be analyzed whether test substances mediate GPCR-mediated dispersion or aggregation of *Xenopus laevis* melanophores. Another test system utilizes the universal adapter G-protein G $\alpha_{\text{h}6}$, which mobilizes $\text{Ca}_{\text{sup.}2+}$. Other screening test systems are described in Lemer et al., supra; WO96/41169; U.S. Pat. No. 5,482,835; WO99/06535; EP 0 939 902; WO99/66326; WO98/34948; EP 0 863 214; U.S. Pat. No. 5,882,944 and U.S. Pat. No. 5,891,641.

10 Therapeutics

Selective polynucleotides, polypeptides, and specific-binding partners thereto, can be utilized in therapeutic applications, especially to treat diseases and conditions described herein. Useful methods include, but are not limited to, immunotherapy (e.g., using specific-binding partners to polypeptides), vaccination (e.g., using a selective polypeptide or a naked DNA encoding such polypeptide), protein or polypeptide replacement therapy, gene therapy (e.g., germ-line correction, antisense), etc.

Various immunotherapeutic approaches can be used. For instance, unlabeled antibody that specifically recognizes a tissue-specific antigen can be used to stimulate the body to destroy or attack a cancer or other diseased tissue, to cause down-regulation, to produce complement-mediated lysis, to inhibit cell growth, etc., of target cells which display the antigen, e.g., analogously to how c-erbB-2 antibodies are used to treat breast cancer. In addition, antibody can be labeled or conjugated to enhance its deleterious effect, e.g., with radionuclides and other energy emitting entities, toxins, such as ricin, exotoxin A (ETA), and diphtheria, cytotoxic or cytostatic agents, immunomodulators, chemotherapeutic agents; etc. See, e.g., U.S. Pat. No. 6,107,090.

An antibody or other specific-binding partner can be conjugated to a second molecule, such as a cytotoxic agent, and used for targeting the second molecule to a tissue-antigen positive cell (Vitetta, E. S. et al., 1993, Immunotoxin therapy, in DeVita, Jr., V. T. et al., eds, Cancer: Principles and Practice of Oncology, 4th ed., J.B. Lippincott Co., Philadelphia, 2624-2636). Examples of cytotoxic agents include, but are not limited to, antimetabolites, alkylating agents, anthracyclines, antibiotics, anti-mitotic agents, radioisotopes and

chemotherapeutic agents. Further examples of cytotoxic agents include, but are not limited to ricin, doxorubicin, daunorubicin, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin D, 1-dehydrotestosterone, diphtheria toxin, *Pseudomonas* exotoxin (PE) A, PE40, abrin, elongation factor-2 and glucocorticoid. Techniques for conjugating therapeutic agents to antibodies are well.

In addition to immunotherapy, polynucleotides and polypeptides can be used as targets for non-immunotherapeutic applications, e.g., using compounds which interfere with function, expression (e.g., antisense as a therapeutic agent), assembly, etc. RNA interference can be used in vitro and in vivo to silence a gene when its expression contributes to a disease (but also for other purposes, e.g., to identify the gene's function to change a developmental pathway of a cell, etc.). See, e.g., Sharp and Zamore, *Science*, 287:2431-2433, 2001; Grishok et al., *Science*, 287:2494, 2001.

Delivery of therapeutic agents can be achieved according to any effective method, including, liposomes, viruses, plasmid vectors, bacterial delivery systems, orally, systemically, etc. Therapeutic agents of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intraperitoneal, topical, transdermal (e.g., using any standard patch), intravenously, ophthalmic, nasally, local, non-oral, such as aerosol, inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive.

In addition to therapeutics, *per se*, the present invention also relates to methods of treating a disease showing altered expression of a tissue selective gene, comprising, e.g., administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of said gene and/or which is effective in treating said disease. The term "treating" is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, etc., of a disease or disorder. By the phrase "altered expression," it is meant that the disease is associated with a mutation in the gene, or any modification to the gene (or corresponding product) which affects its normal function. Thus, expression refers to, e.g., transcription, translation, splicing, stability of the mRNA or protein product, activity of the gene product, differential

expression, etc.

Any agent which "treats" the disease can be used. Such an agent can be one which regulates the expression of a tissue selective gene. Expression refers to the same acts already mentioned, e.g. transcription, translation, splicing, stability of the mRNA or protein product, activity of the gene product, differential expression, etc. For instance, if the condition was a result of a complete deficiency of the gene product, administration of gene product to a patient would be said to treat the disease and regulate the gene's expression. Many other possible situations are possible, e.g., where the gene is aberrantly expressed, and the therapeutic agent regulates the aberrant expression by restoring its normal expression pattern.

Antisense

Antisense polynucleotide (e.g., RNA) can also be prepared from a polynucleotide according to the present invention. Antisense polynucleotide can be used in various ways, such as to regulate or modulate expression of the polypeptides they encode, e.g., inhibit their expression, for in situ hybridization, for therapeutic purposes, for making targeted mutations (in vivo, triplex, etc.) etc. For guidance on administering and designing anti-sense, see, e.g., U.S. Pat. Nos. 6,200,960, 6,200,807, 6,197,584, 6,190,869, 6,190,661, 6,187,587, 6,168,950, 6,153,595, 6,150,162, 6,133,246, 6,117,847, 6,096,722, 6,087,343, 6,040,296, 6,005,095, 5,998,383, 5,994,230, 5,891,725, 5,885,970, and 5,840,708. An antisense polynucleotides can be operably linked to an expression control sequence. A total length of about 35 bp can be used in cell culture with cationic liposomes to facilitate cellular uptake, but for *in vivo* use, preferably shorter oligonucleotides are administered, e.g. 25 nucleotides.

Antisense polynucleotides can comprise modified, nonnaturally-occurring nucleotides and linkages between the nucleotides (e.g., modification of the phosphate-sugar backbone; methyl phosphonate, phosphorothioate, or phosphorodithioate linkages; and 2'-O-methyl ribose sugar units), e.g., to enhance in vivo or in vitro stability, to confer nuclease resistance, to modulate uptake, to modulate cellular distribution and compartmentalization, etc. Any effective nucleotide or modification can be used, including those already mentioned, as known in the art, etc., e.g., disclosed in U.S. Pat. Nos. 6,133,438; 6,127,533; 6,124,445; 6,121,437; 5,218,103 (e.g., nucleoside thiophosphoramidites); 4,973,679; Sproat et al., "2'-O-Methyloligoribonucleotides: synthesis and applications," Oligonucleotides and Analogs A

Practical Approach, Eckstein (ed.), IRL Press, Oxford, 1991, 49-86; Iribarren et al., "2'-O-Alkyl Oligoribonucleotides as Antisense Probes," Proc. Natl. Acad. Sci. USA, 1990, 87, 7747-7751; Cotton et al., "2'-O-methyl, 2'-O-ethyl oligoribonucleotides and phosphorothioate oligodeoxyribonucleotides as inhibitors of the in vitro U7 snRNP-dependent mRNA processing event," Nucl. Acids Res., 1991, 19, 2629-2635.

Arrays

The present invention also relates to an ordered array of polynucleotide probes and specific-binding partners (e.g., antibodies) for detecting the expression of tissue selective genes or polypeptides encoded thereby, in a sample, comprising, one or more polynucleotide probes or specific binding partners associated with a solid support or in separate receptacles, wherein each probe is specific for a tissue selective gene or a specific-binding partner which is specific for a polypeptide.

The phrase "ordered array" indicates that the probes are arranged in an identifiable or position-addressable pattern, e.g., such as the arrays disclosed in U.S. Pat. Nos. 6,156,501, 6,077,673, 6,054,270, 5,723,320, 5,700,637, WO9919711, WO00023803. The probes are associated with the solid support in any effective way. For instance, the probes can be bound to the solid support, either by polymerizing the probes on the substrate, or by attaching a probe to the substrate. Association can be, covalent, electrostatic, noncovalent, hydrophobic, hydrophilic, noncovalent, coordination, adsorbed, absorbed, polar, etc. When fibers or hollow filaments are utilized for the array, the probes can fill the hollow orifice, be absorbed into the solid filament, be attached to the surface of the orifice, etc. Probes can be of any effective size, sequence identity, composition, etc., as already discussed.

Transgenic animals

The present invention also relates to transgenic animals comprising tissue selective genes, and homologs thereof. (Methods of making transgenic animals, and associated recombinant technology, can be accomplished conventionally, e.g., as described in *Transgenic Animal Technology*, Pinkert et al., 2nd Edition, Academic Press, 2002.) Such genes, as discussed in more detail below, include, but are not limited to, functionally-disrupted genes, mutated genes, ectopically or selectively-expressed genes, inducible or

regulatable genes, etc. These transgenic animals can be produced according to any suitable technique or method, including homologous recombination, mutagenesis (e.g., ENU, Rathkolb et al., *Exp. Physiol.*, 85(6):635-644, 2000), and the tetracycline-regulated gene expression system (e.g., U.S. Pat. No. 6,242,667). The term "gene" as used herein includes
5 any part of a gene, i.e., regulatory sequences, promoters, enhancers, exons, introns, coding sequences, etc. The nucleic acid present in the construct or transgene can be naturally-occurring wild-type, polymorphic, or mutated. Where the animal is a non-human animal, its homolog can be used instead. Transgenic animals can have structural and/or functional defects in any of the tissues described herein, e.g., pancreas, kidney, retina, and immune cells,
10 as well as having or being susceptible to any of the associated disorders or diseases mentioned herein.

Along these lines, polynucleotides of the present invention can be used to create transgenic animals, e.g. a non-human animal, comprising at least one cell whose genome comprises a functional disruption of one or tissue selective genes, or homologs thereof (e.g.,
15 a mouse homolog when a mouse is used). By the phrases "functional disruption" or "functionally disrupted," it is meant that the gene does not express a biologically-active product. It can be substantially deficient in at least one functional activity coded for by the gene. Expression of a polypeptide can be substantially absent, i.e., essentially undetectable amounts are made. However, polypeptide can also be made, but which is deficient in
20 activity, e.g., where only an amino-terminal portion of the gene product is produced.

The transgenic animal can comprise one or more cells. When substantially all its cells contain the engineered gene, it can be referred to as a transgenic animal "whose genome comprises" the engineered gene. This indicates that the endogenous gene loci of the animal has been modified and substantially all cells contain such modification.

25 Functional disruption of the gene can be accomplished in any effective way, including, e.g., introduction of a stop codon into any part of the coding sequence such that the resulting polypeptide is biologically inactive (e.g., because it lacks a catalytic domain, a ligand binding domain, etc.), introduction of a mutation into a promoter or other regulatory sequence that is effective to turn it off, or reduce transcription of the gene, insertion of an
30 exogenous sequence into the gene which inactivates it (e.g., which disrupts the production of a biologically-active polypeptide or which disrupts the promoter or other transcriptional

machinery), deletion of sequences from the gene (or homolog thereof), etc. Examples of transgenic animals having functionally disrupted genes are well known, e.g., as described in U.S. Pat. Nos. 6,239,326, 6,225,525, 6,207,878, 6,194,633, 6,187,992, 6,180,849, 6,177,610, 6,100,445, 6,087,555, 6,080,910, 6,069,297, 6,060,642, 6,028,244, 6,013,858, 5,981,830, 5,866,760, 5,859,314, 5,850,004, 5,817,912, 5,789,654, 5,777,195, and 5,569,824. A transgenic animal which comprises the functional disruption can also be referred to as a "knock-out" animal, since the biological activity of its gene has been "knocked-out." Knock-outs can be homozygous or heterozygous.

For creating functionally disrupted genes, and other gene mutations, homologous recombination technology is of special interest since it allows specific regions of the genome to be targeted. Using homologous recombination methods, genes can be specifically-inactivated, specific mutations can be introduced, and exogenous sequences can be introduced at specific sites. These methods are well known in the art, e.g., as described in the patents above. See, also, Robertson, *Biol. Reproduc.*, 44(2):238-245, 1991. Generally, the genetic engineering is performed in an embryonic stem (ES) cell, or other pluripotent cell line (e.g., adult stem cells, EG cells), and that genetically-modified cell (or nucleus) is used to create a whole organism. Nuclear transfer can be used in combination with homologous recombination technologies. For example, a gene locus can be disrupted in mouse ES cells using a positive-negative selection method (e.g., Mansour et al., *Nature*, 336:348-352, 1988). In this method, a targeting vector can be constructed which comprises a part of the gene to be targeted. A selectable marker, such as neomycin resistance genes, can be inserted into an exon present in the targeting vector, disrupting it. When the vector recombines with the ES cell genome, it disrupts the function of the gene. The presence in the cell of the vector can be determined by expression of neomycin resistance. See, e.g., U.S. Pat. No. 6,239,326. Cells having at least one functionally disrupted gene can be used to make chimeric and germline animals, e.g., animals having somatic and/or germ cells comprising the engineered gene. Homozygous knock-out animals can be obtained from breeding heterozygous knock-out animals. See, e.g., U.S. Pat. No. 6,225,525.

The present invention also relates to non-human, transgenic animal whose genome comprises recombinant tissue selective nucleic acid (and homologs thereof) operatively linked to an expression control sequence effective to express said coding sequence in a target

tissue. Such a transgenic animal can also be referred to as a "knock-in" animal since an exogenous gene has been introduced, stably, into its genome. "Operable linkage" has the meaning used through the specification, i.e., placed in a functional relationship with another nucleic acid. When a gene is operably linked to an expression control sequence, as explained
5 above, it indicates that the gene (e.g., coding sequence) is joined to the expression control sequence (e.g., promoter) in such a way that facilitates transcription and translation of the coding sequence. As described above, the phrase "genome" indicates that the genome of the cell has been modified. In this case, the recombinant gene has been stably integrated into the genome of the animal. The nucleic acid (e.g., a coding sequence) in operable linkage with
10 the expression control sequence can also be referred to as a construct or transgene.

Any expression control sequence can be used depending on the purpose. For instance, if selective expression is desired, then expression control sequences which limit its expression can be selected. These include, e.g., tissue or cell-specific promoters, introns, enhancers, etc. For various methods of cell and tissue-specific expression, see, e.g., U.S. Pat.
15 Nos. 6,215,040, 6,210,736, and 6,153,427. These also include the endogenous promoter, i.e., the coding sequence can be operably linked to its own promoter. Inducible and regulatable promoters can also be utilized.

The present invention also relates to a transgenic animal which contains a functionally disrupted and a transgene stably integrated into the animals genome. Such an animal can be
20 constructed using combinations any of the above- and below-mentioned methods. Such animals have any of the aforementioned uses, including permitting the knock-out of the normal gene and its replacement with a mutated gene. Such a transgene can be integrated at the endogenous gene locus so that the functional disruption and "knock-in" are carried out in the same step.

25 In addition to the methods mentioned above, transgenic animals can be prepared according to known methods, including, e.g., by pronuclear injection of recombinant genes into pronuclei of 1-cell embryos, incorporating an artificial yeast chromosome into embryonic stem cells, gene targeting methods, embryonic stem cell methodology, cloning methods, nuclear transfer methods. See, also, e.g., U.S. Patent Nos. 4,736,866; 4,873,191;
30 4,873,316; 5,082,779; 5,304,489; 5,174,986; 5,175,384; 5,175,385; 5,221,778; Gordon et al., Proc. Natl. Acad. Sci., 77:7380-7384, 1980; Palmiter et al., Cell, 41:343-345, 1985; Palmiter

et al., *Ann. Rev. Genet.*, 20:465-499, 1986; Askew et al., *Mol. Cell. Bio.*, 13:4115-4124, 1993; Games et al. *Nature*, 373:523-527, 1995; Valancius and Smithies, *Mol. Cell. Bio.*, 11:1402-1408, 1991; Stacey et al., *Mol. Cell. Bio.*, 14:1009-1016, 1994; Hasty et al., *Nature*, 350:243-246, 1995; Rubinstein et al., *Nucl. Acid Res.*, 21:2613-2617, 1993; Cibelli et al.,
 5 Science, 280:1256-1258, 1998. For guidance on recombinase excision systems, see, e.g., U.S. Pat. Nos. 5,626,159, 5,527,695, and 5,434,066. See also, Orban, P.C., et al., "Tissue- and Site-Specific DNA Recombination in Transgenic Mice," *Proc. Natl. Acad. Sci. USA*, 89:6861-6865 (1992); O'Gorman, S., et al., "Recombinase-Mediated Gene Activation and Site-Specific Integration in Mammalian Cells," *Science*, 251:1351-1355 (1991); Sauer, B., et
 10 al., "Cre-stimulated recombination at loxP-Containing DNA sequences placed into the mammalian genome," *Polynucleotides Research*, 17(1):147-161 (1989); Gagneten, S. et al. (1997) *Nucl. Acids Res.* 25:3326-3331; Xiao and Weaver (1997) *Nucl. Acids Res.* 25:2985-2991; Agah, R. et al. (1997) *J. Clin. Invest.* 100:169-179; Barlow, C. et al. (1997) *Nucl. Acids Res.* 25:2543-2545; Araki, K. et al. (1997) *Nucl. Acids Res.* 25:868-872; Mortensen,
 15 R. N. et al. (1992) *Mol. Cell. Biol.* 12:2391-2395 (G418 escalation method); Lakhani, P. P. et al. (1997) *Proc. Natl. Acad. Sci. USA* 94:9950-9955 ("hit and run"); Westphal and Leder (1997) *Curr. Biol.* 7:530-533 (transposon-generated "knock-out" and "knock-in"); Templeton, N. S. et al. (1997) *Gene Ther.* 4:700-709 (methods for efficient gene targeting, allowing for a high frequency of homologous recombination events, e.g., without selectable
 20 markers); PCT International Publication WO 93/22443 (functionally-disrupted).

A polynucleotide according to the present invention can be introduced into any non-human animal, including a non-human mammal, mouse (Hogan et al., Manipulating the Mouse Embryo: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1986), pig (Hammer et al., *Nature*, 315:343-345, 1985), sheep (Hammer et al.,
 25 *Nature*, 315:343-345, 1985), cattle, rat, or primate. See also, e.g., Church, 1987, *Trends in Biotech.* 5:13-19; Clark et al., *Trends in Biotech.* 5:20-24, 1987); and DePamphilis et al., *BioTechniques*, 6:662-680, 1988. Transgenic animals can be produced by the methods described in U.S. Pat. No. 5,994,618, and utilized for any of the utilities described therein.

30 Database

The present invention also relates to electronic forms of polynucleotides,

polypeptides, etc., of the present invention, including computer-readable medium (e.g., magnetic, optical, etc., stored in any suitable format, such as flat files or hierarchical files) which comprise such sequences, or fragments thereof, e-commerce-related means, etc.

Along these lines, the present invention relates to methods of retrieving nucleic acid and/or

- 5 polypeptide sequences from a computer-readable medium, comprising, one or more of the following steps in any effective order, e.g., selecting a cell or gene expression profile, e.g., a profile that specifies that said gene is differentially expressed in a tissue as described herein, and retrieving said differentially expressed nucleic acid or polypeptide.

- 10 A "gene expression profile" means the list of tissues, cells, etc., in which a defined gene is expressed (i.e, transcribed and/or translated). A "cell expression profile" means the genes which are expressed in the particular cell type. The profile can be a list of the tissues in which the gene is expressed, but can include additional information as well, including level of expression (e.g., a quantity as compared or normalized to a control gene), and information on temporal (e.g., at what point in the cell-cycle or developmental program) and
- 15 spatial expression. By the phrase "selecting a gene or cell expression profile," it is meant that a user decides what type of gene or cell expression pattern he is interested in retrieving, e.g., he may require that the gene is differentially expressed in a tissue, or he may require that the gene is not expressed in blood, but must be expressed in pancreas. Any pattern of expression preferences may be selected. The selecting can be performed by any effective method. In
- 20 general, "selecting" refers to the process in which a user forms a query that is used to search a database of gene expression profiles. The step of retrieving involves searching for results in a database that correspond to the query set forth in the selecting step. Any suitable algorithm can be utilized to perform the search query, including algorithms that look for matches, or that perform optimization between query and data. The database is information that has been
- 25 stored in an appropriate storage medium, having a suitable computer-readable format. Once results are retrieved, they can be displayed in any suitable format, such as HTML.

- For instance, the user may be interested in identifying genes that are differentially expressed in a pancreas or kidney. He may not care whether small amounts of expression occur in other tissues, as long as such genes are not expressed in peripheral blood
- 30 lymphocytes. A query is formed by the user to retrieve the set of genes from the database

having the desired gene or cell expression profile. Once the query is inputted into the system, a search algorithm is used to interrogate the database, and retrieve results.

Advertising, licensing, etc., methods

5 The present invention also relates to methods of advertising, licensing, selling, purchasing, brokering, etc., genes, polynucleotides, specific-binding partners, antibodies, etc., of the present invention. Methods can comprises, e.g., displaying tissue selective polynucleotide or polypeptide sequences, or antibody specific thereto, in a printed or computer-readable medium (e.g., on the Web or Internet), accepting an offer to purchase said
10 gene, polypeptide, or antibody.

Other

 A polynucleotide, probe, polypeptide, antibody, specific-binding partner, etc., according to the present invention can be isolated. The term "isolated" means that the
15 material is in a form in which it is not found in its original environment or in nature, e.g., more concentrated, more purified, separated from component, etc. An isolated polynucleotide includes, e.g., a polynucleotide having the sequenced separated from the chromosomal DNA found in a living animal, e.g., as the complete gene, a transcript, or a cDNA. This polynucleotide can be part of a vector or inserted into a chromosome (by
20 specific gene-targeting or by random integration at a position other than its normal position) and still be isolated in that it is not in a form that is found in its natural environment. A polynucleotide, polypeptide, etc., of the present invention can also be substantially purified. By substantially purified, it is meant that polynucleotide or polypeptide is separated and is essentially free from other polynucleotides or polypeptides, i.e., the polynucleotide or
25 polypeptide is the primary and active constituent. A polynucleotide can also be a recombinant molecule. By "recombinant," it is meant that the polynucleotide is an arrangement or form which does not occur in nature. For instance, a recombinant molecule comprising a promoter sequence would not encompass the naturally-occurring gene, but would include the promoter operably linked to a coding sequence not associated with it in
30 nature, e.g., a reporter gene, or a truncation of the normal coding sequence.

The term "marker" is used herein to indicate a means for detecting or labeling a target. A marker can be a polynucleotide (usually referred to as a "probe"), polypeptide (e.g., an antibody conjugated to a detectable label), PNA, or any effective material.

The topic headings set forth above are meant as guidance where certain information
5 can be found in the application, but are not intended to be the only source in the application where information on such topic can be found. Reference materials

For other aspects of the polynucleotides, reference is made to standard textbooks of molecular biology. See, e.g., Hames et al., Polynucleotide Hybridization, IL Press, 1985; Davis et al., Basic Methods in Molecular Biology, Elsevir Sciences Publishing, Inc., New
10 York, 1986; Sambrook et al., Molecular Cloning, CSH Press, 1989; Howe, Gene Cloning and Manipulation, Cambridge University Press, 1995; Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., 1994-1998.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following
15 preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. The entire disclosure of all applications, patents and publications, cited above and in the figures are hereby incorporated by reference in their entirety, including U.S. Application Serial Nos. 60/372,669 April 16, 2003, 60/374,823 filed April 24, 2002, 60/376,558 filed May 1, 2002, 60/381,366
20 filed May 20, 2002, 60/403,648 filed August 16, 2002, 60/411,882 filed September 20, 2002, and 60/424,336 filed November 7, 2002.

TABLE 1

Clone ID (gene code)	ACCN	Predominant sites of expression	Other expression sites	Cytogenetic sites
TMD0024	XM_060945	thymus	none	1q22
TMD1779	XM_060946	thymus and PBL	none	1q22
TMD0884	XM_060947	thymus	skin and ovary	1q22
TMD0025	XM_060948	thymus	none	1q22
TMD1780	XM_089422	thymus	none	1q22
TMD1781	XM_089421	PBL	thymus	1q22
TMD0304	XM_060956	bone marrow and muscle	testis	1q22
TMD0888	XM_060957	bone marrow	lung, muscle and testis	1q22
TMD0890	XM_060959	bone marrow	lung and PBL	1q22

TABLE 2

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Clone ID (gene code)	ACCN	Protein seq length	Domain Description
TMD1779	XM_060946	264	Transmembrane domain: 26 - 48 Transmembrane domain: 55 - 77 Transmembrane domain: 92 - 114 Transmembrane domain: 134 - 156 Transmembrane domain: 197 - 219
TMD0024	XM_060945	268	Transmembrane domain: 16 - 38 Transmembrane domain: 53 - 75 Transmembrane domain: 96 - 118 Transmembrane domain: 156 - 178 Transmembrane domain: 191 - 213 Transmembrane domain: 228 - 246
TMD0025	XM_060948	313	Transmembrane domain: 29 - 51 Transmembrane domain: 58 - 77 Transmembrane domain: 92 - 114 Transmembrane domain: 135 - 157 Transmembrane domain: 197 - 219 Transmembrane domain: 240 - 262 Transmembrane domain: 272 - 294
TMD0304	XM_060956	319	Transmembrane domain: 28 - 50 Transmembrane domain: 63 - 82 Transmembrane domain: 102 - 124 Transmembrane domain: 144 - 166 Transmembrane domain: 205 - 227 Transmembrane domain: 240 - 262 Transmembrane domain: 272 - 294
TMD0884	XM_060947	299	Transmembrane domain: 20 - 42 Transmembrane domain: 54 - 76 Transmembrane domain: 91 - 113 Transmembrane domain: 126 - 148

-95-

				Transmembrane domain: 183 - 205
				Transmembrane domain: 226 - 248
				Transmembrane domain: 258 - 277
5	TMD0888	XM_060957	312	Transmembrane domain: 25 - 47
				Transmembrane domain: 59 - 78
				Transmembrane domain: 98 - 120
				Transmembrane domain: 141 - 163
10				Transmembrane domain: 207 - 229
				Transmembrane domain: 241 - 260
				Transmembrane domain: 270 - 292
	TMD0890	XM_060959	280	Transmembrane domain: 26 - 48
15				Transmembrane domain: 122 - 144
				Transmembrane domain: 180 - 202
				Transmembrane domain: 215 - 237
				Transmembrane domain: 252 - 269
	TMD1780	XM_089422	491	Transmembrane domain: 20 - 42
20				Transmembrane domain: 54 - 76
				Transmembrane domain: 91 - 113
				Transmembrane domain: 137 - 159
				Transmembrane domain: 190 - 212
25				Transmembrane domain: 231 - 253
				Transmembrane domain: 266 - 283
				Transmembrane domain: 304 - 326
				Transmembrane domain: 336 - 358
				Transmembrane domain: 379 - 401
30				Transmembrane domain: 437 - 459
	TMD1781	XM_089421	91	Transmembrane domain: 63 - 85
35				

-96-

	TMD0024 XM_060945	TMD1779 XM_060946	TMD0884 XM_060947	TMD0025 XM_060948	TMD1780 XM_089422	TMD1781 XM_089421	TMD0304 XM_060956	TMD0888 XM_060957
TMD0024 XM_060945								
TMD1779 XM_060946	no significant similarity							
TMD0884 XM_060947	74%(371nt)	no significant similarity						
TMD0025 XM_060948	71%(222nt) 80%(73nt)	90%(605nt)	83%(54nt)					
TMD1780 XM_089422	81%(114nt) 74%(186nt) 79%(113nt) 77%(99nt)	83%(71nt)	78%(90nt)	80%(84nt)				
TMD1781 XM_089421	91%(35nt) 77%(80nt)	no significant similarity	no significant similarity	no significant similarity	77%(179nt) 82%(46nt)			
TMD0304 XM_060956	no significant similarity	no significant similarity	no significant similarity	no significant similarity	84%(39nt)	no significant similarity		
TMD0888 XM_060957	no significant similarity	no significant similarity	no significant similarity	84%(38nt)	no significant similarity	no significant similarity	73%(241nt)	
TMD0890 XM_060959	no significant similarity	no significant similarity	no significant similarity	no significant similarity	no significant similarity	no significant similarity	no significant similarity	84%(39nt)

TABLE 3

-97-

	TMD0024 XP_060945	TMD1779 XP_060946	TMD0884 XP_060947	TMD0025 XP_060948	TMD1780 XP_089422	TMD1781 XP_089421	TMD0304 XP_060956	TMD0888 XP_060957
TMD0024 XP_060945								
TMD1779 XP_060946	47%(200aa)							
TMD0884 XP_060947	62%(171aa)	36%(92aa)						
TMD0025 XP_060948	53%(252aa)	73%(233aa)	46%(166aa)					
TMD1780 XP_089422	59%(261aa) 59%(181aa)	46%(227aa) 46%(169aa)	55%(165aa) 47%(111aa)	52%(300aa)				
TMD1781 XP_089421	40%(94aa)	35%(82aa)	52%(40aa)	37%(94aa)	51%(93aa) 49%(77aa)			
TMD0304 XP_060956	40%(257aa)	37%(229aa)	36%(163aa)	39%(299aa)	39%(300aa)	34%(89aa)		
TMD0888 XP_060957	49%(251aa)	37%(239aa)	41%(157aa)	40%(305aa)	45%(304aa) 43%(189aa)	41%(82aa)	50%(301aa)	
TMD0890 XP_060959	41%(196)	32%(132aa)	32%(156aa)	36%(179aa)	42%(200aa)	38%(72aa)	36%(196aa)	46%(196aa)

TABLE 4

-99-

TABLE 5

CLONE ID	Forward	Reverse	PROMOTER
TMD179 (SEQ ID NO 1-2)	GGTCAATGAGACTGTGG TGAGAGAGGTCATCT (SEQ ID NO 3)	CTATCACTCCCAAGTGGAA GGAAACTGAAG (SEQ ID NO 4)	CTCTTCAGATTAAATGGCCAGACTAGTTTATGTGGTGCGAGACATT (SEQ ID NO 5)
TMD024 (SEQ ID NO 6-7)	CCAGCTGCTCAGACA CCAAAGACC (SEQ ID NO 8)	GGCACCATAATTACCAGGAT GCTGAGG (SEQ ID NO 9)	GAGTGCCAAATATATAAGAGGTTATGTTCAA TGCAACATGTTAAATGCCAA (SEQ ID NO 10) ACTCTTAGATATAAAGGGGAGAGTTTATAAAGAACCCCTGATTAAATCA (SEQ ID NO 11)
TMD025 (SEQ ID NO 12-13)	CCTGTTCACTCTGGGCA CCAATGC (SEQ ID NO 14)	CTGGTTGGAGGAGTGAAG GGCAG (SEQ ID NO 15)	TAATCTATGTAAAAATGCCACTGGAGTAGAATCAGCTGTCTCTCATGTGCC (SEQ ID NO 19) TACCTTCTGTATATAAAAAATATACTAATAACACACACACACTCATACAC (SEQ ID NO 16) CTTCAGAGTATATAAATGAAGCTGGATACCAAGCAAGACATCTGGATG (SEQ ID NO 17) CCCTTGGAGATATAAAAAATGCCAGTAAATAGATGTGTGCTCACAATCTT (SEQ ID NO 18)
TMD0304 (SEQ ID NO 20-21)	CTGTATGTTCCCGCATGC GCACAG (SEQ ID NO 22)	GCAAGGTGGAATCCATGCA ATCTCAG (SEQ ID NO 23)	AGACAGCGTTAAAAATGACCAAACTACAGAAAAATATTTCCAGATAAT (SEQ ID NO 24)
TMD0884 (SEQ ID NO 25-26)	TGTCAATATCTGTTGTT CAGTGTGCTCC (SEQ ID NO 27)	CATCTACCCAGAACCTTTCT CAGAGCCATC (SEQ ID NO 28)	GTCACTGGTGTATAAGCAGCGAGTGCACAAAGGAAATATTAACACTAGAACC (SEQ ID NO 29) TTCTTCATTATAACATCAGGGGGCTTGGCTAGATATTTAACAGCTGC (SEQ ID NO 30) GCTAGATATTAACAGCTGCTGTATGAGAGAGCTGGGTACATCACTTTTACTGTGTTT (SEQ ID NO 31) ATTCAGTTATGTATATGAGAGAGCTGGGTACATCACTTTTACTGTGTTT (SEQ ID NO 32)
TMD0888 (SEQ ID NO 33-34)	GGAAGTGAGCCAGGTA GCAGAAATCATC (SEQ ID NO 35)	GGAGCAGAGGATCAGCAGG AAGGTG (SEQ ID NO 36)	ACACTGCACTTATATAGGTGGCCAGGTAGTTGAGCTGGTGAATTTGA (SEQ ID NO 37) GCACGTGACATTAAAGGATGGGGCATGGAGGAGAACTAAAGTTGGAG (SEQ ID NO 38) ATTCAAATTATATATTTGTCCAGTACGGTATCAATATATATTCAGTA (SEQ ID NO 39)
TMD0890 (SEQ ID NO 40-41)	TCACCACCACTGGGACC GTACAACCT (SEQ ID NO 42)	GGCCACACCAATCACTGTGG CAT (SEQ ID NO 43)	CAATCTGTTATTTATACGGCCTCTACATCCATCCAGTACCTGCTTATGTA (SEQ ID NO 44) GTTCTCTTTTATAAAGGCTATGTGGGACTTGCACAACTTCTAGTGGCC (SEQ ID NO 45) CAACATGAATATAGTATGGGGAGTATCTTGGGTAGAAAGGATGCCGAG (SEQ ID NO 46)
TMD1780 (SEQ ID NO 47-48)	CTCTGAATCTTCTACAC AACTGTTATCTGCCCA (SEQ ID NO 49)	ATGAGATGGGAAGCACAGGT GGAGAAG (SEQ ID NO 50)	ATCAATATGTTAAAAATGGCCGTACTGTCAAAAGCAAATTTACAGATTCAA (SEQ ID NO 51) ATATGAACCAACAAAAAGCCCTCAAAATAGCCCAAGTAACCCCTAAAGAAAA (SEQ ID NO 52) CGCCCTATTCATAAATGTTGGGAAATAGCTGGCTAGCCATCTGCAGAA (SEQ ID NO 53) CATAGGGTCTTAAAAATGGGAGAGAGAAATCAGAAAAATCAGAGAGAAAGAG (SEQ ID NO 54)
TMD1781 (SEQ ID NO 55-56)	ATGACAGTTTATGATTCC TATGTGCCATCTGC (SEQ ID NO 57)	TCAGGATGGTGTGAACAATG AAGCCATAG (SEQ ID NO 58)	TTCCCTATTTAATAATGTTGTTGGGAAAACTGGCTAGCCATATGTAGAA (SEQ ID NO 59) AACAACCCCATCAAAAGTGGGGCCCAAGATATGAACAGACACTTCTCAAA (SEQ ID NO 60) AATGGCGATCAATAAAGAGTCAAGAAACAAACAGGTGCTGGAGAGGATGTG (SEQ ID NO 61) CCGAGAGGATTAATAATCATGTGCTGTAAAGACACATGCCCACTGATGT (SEQ ID NO 62)

-100-

TABLE 6

SEQ ID NO	GENE NUMBER	GENBANK IDENTIFIER	PREDOMINANT SITES OF EXPRESSION	PROMOTER (SEQ ID NO)	PRIMER (FOR, REV) (SEQ ID NO)
63,64	TMD0785	XM 060310	kidney	65-68	69,70

	XM_062147	XM_061676
outside	1-27	1-28
TM (1)	28-50	29-51
inside	51-61	52-62
TM (2)	62-84	63-85
outside	85-98	86-99
TM (3)	99-121	100-122
inside	122-140	123-133
TM (4)	141-163	134-156
outside	164-203	157-201
TM (5)	204-226	202-224
inside	227-237	225-236
TM (6)	238-260	237-259
outside	261-274	260-273
TM (7)	275-293	274-296
inside	294-313	297-314

TABLE 7

-101-

Clone ID (gene code)	Accession	Gene Name/Description	Predominant tissue/ expression	Other expression sites
TMD0049	XM_057351	Homo sapiens similar to organic anion transporter 4 like protein (LOC116085) mRNA	kidney	none
TMD0190	XM_087157	Homo sapiens similar to sodium-coupled ascorbic acid transporter 2 (LOC151295) mRNA	kidney	colon and liver
TMD0242	XM_088369	Homo sapiens similar to unnamed protein product (LOC157724) mRNA	kidney	none
TMD0335	XM_089960	Homo sapiens similar to sodium iodide symporter (LOC159963) mRNA	kidney	adrenal gland, heart, intestine (small), liver, muscle, testis
TMD0371 (new)	XM_089732	Homo sapiens similar to CG8271 gene product (LOC196023) mRNA	kidney	pancreas and testis
TMD0374 (new)	XM_085595	Homo sapiens similar to unnamed protein product (LOC148802) mRNA	kidney	brain, muscle, ovary, skin, testis
TMD0469	XM_038736	Homo sapiens solute carrier family 4 sodium bicarbonate cotransporter member 9 (SLC4A9) mRNA	kidney	none
TMD0719	XM_059548	Homo sapiens hypothetical gene supported by XM_059548 (LOC131920) mRNA	kidney	none
TMD0731	XM_059703	Homo sapiens similar to putative (H. sapiens) (LOC134288) mRNA	kidney	adrenal gland, muscle, thyroid
TMD0785	XM_060310	Homo sapiens similar to olfactory receptor MOR275-2 (LOC127069) mRNA	kidney	none
TMD0841	XM_060623	Homo sapiens similar to KIAA0711 gene product (H. sapiens) (LOC127707) mRNA	kidney	lung
TMD1114	NM_019841	Homo sapiens transient receptor potential cation channel subfamily V member 5 (TRPV5) mRNA	kidney	none
TMD1148	XM_087108	Homo sapiens similar to calcium channel voltage-dependent gamma subunit 6 (LOC151151) mRNA	kidney	none

TABLE 8

-102-

TABLE 9

Gene Code	SEQ ID NO	Protein seq length(aa)	domain description
TMD0049	2	332	Sugar (and other) transporter: 2 - 302 Transmembrane domain: 12 - 34 Transmembrane domain: 39 - 58 Transmembrane domain: 131 - 153 Transmembrane domain: 157 - 179 Transmembrane domain: 186 - 205 Transmembrane domain: 215 - 237
TMD0190	4	243	Permease family: 91 - 224
TMD0242	6	470	AA-permease: 27 - 356 Transmembrane domain: 13 - 35 Transmembrane domain: 50 - 72 Transmembrane domain: 93 - 115 Transmembrane domain: 137 - 154 Transmembrane domain: 161 - 183 Transmembrane domain: 207 - 229 Transmembrane domain: 242 - 264 Transmembrane domain: 286 - 308 Transmembrane domain: 335 - 357 Transmembrane domain: 362 - 379 Transmembrane domain: 392 - 414 Transmembrane domain: 420 - 442

-103-

TMD0335	8	178	Sodium solute symporter family: 41 - 172
TMD0371	10	516	Transmembrane domain: 45 - 67
			Transmembrane domain: 87 - 109
			Transmembrane domain: 116 - 138
			Transmembrane domain: 143 - 165
			Transmembrane domain: 174 - 196
			Transmembrane domain: 201 - 223
			Transmembrane domain: 283 - 305
			Transmembrane domain: 320 - 339
			Transmembrane domain: 351 - 370
			Transmembrane domain: 375 - 397
			Transmembrane domain: 404 - 426
			Transmembrane domain: 441 - 463
TMD0374	12	566	Transmembrane domain: 31 - 53
			Transmembrane domain: 68 - 90
			Transmembrane domain: 116 - 138
			Transmembrane domain: 153 - 171
			Transmembrane domain: 184 - 206
			Transmembrane domain: 211 - 233
			Transmembrane domain: 254 - 273
			Transmembrane domain: 288 - 310
			Transmembrane domain: 331 - 353
			Transmembrane domain: 373 - 395
			Transmembrane domain: 404 - 426
			Transmembrane domain: 431 - 453
			Transmembrane domain: 542 - 564

-104-

TMD0469	14	983	HCO3- transporter family: 108 - 891
			Transmembrane domain: 413 - 435
			Transmembrane domain: 447 - 469
			Transmembrane domain: 498 - 520
			Transmembrane domain: 532 - 554
			Transmembrane domain: 623 - 645
			Transmembrane domain: 665 - 684
			Transmembrane domain: 712 - 731
			Transmembrane domain: 751 - 773
			Transmembrane domain: 813 - 832
			Transmembrane domain: 839 - 858
			Transmembrane domain: 897 - 919
TMD0719	16	146	Transmembrane domain: 7 - 29
			Transmembrane domain: 49 - 71
TMD0731	18	218	Transmembrane domain: 38 - 60
			Transmembrane domain: 70 - 92
TMD0785	20	312	7 transmembrane receptor (rhodopsin family): 58 - 290
			Transmembrane domain: 29 - 51
			Transmembrane domain: 61 - 83
			Transmembrane domain: 140 - 162
			Transmembrane domain: 197 - 219
			Transmembrane domain: 240 - 262
			Transmembrane domain: 272 - 294
TMD0841	22	1161	Kelch motif: 850 - 895
			Kelch motif: 897 - 938

-105-

TMD1114	24	729		Transmembrane domain: 327 - 349
				Transmembrane domain: 383 - 405
				Transmembrane domain: 420 - 438
				Transmembrane domain: 451 - 473
				Transmembrane domain: 493 - 512
				Transmembrane domain: 519 - 541
				Transmembrane domain: 554 - 576
TMD1148	26	103		Transmembrane domain: 7 - 24
				Transmembrane domain: 39 - 61
				Transmembrane domain: 68 - 90

-106-

Gene ID (gene code)	ACCN	Cytogenetic locus	Disease/Linkage
TMD0049	XM_057351	11q12.1	osteoporosis-pseudoglioma syndrome; spastic paraplegia 1 7
TMD0190	XM_087157	2q36.2	none
TMD0242	XM_088369	8q21.2	none
TMD0335	XM_089960	11p14.2	none
TMD0371A	XM_089732	10q23.33	epilepsy, partial, with auditory features; spastic paraplegia 9, autosomal dominant
TMD0374	XM_085595	17p11.2	smith-magenis syndrome
TMD0469	XM_038736	5q31	paget disease of bone 4
TMD0719	XM_059548	3q29	none
TMD0731	XM_059703	5q13.2	spastic paraplegia 11, autosomal recessive; corpus callosum, agenesis of, with neuropathy
TMD0785	XM_060310	1q44-tel	familial cold urticaria (FCU); Muckle-Wells syndrome (MWS); prostate cancer susceptibility
TMD0841	XM_060623	1p36.13	breast cancer, ductal, 2; prostate cancer/brain cancer susceptibility; melanoma, cutaneous
TMD1114	NM_019841	7q35	glaucoma 1, open angle, f
TMD1148	XM_087108	2q14.1	motor neuropathy, distal hereditary, with vocal cord paralysis; cardiomyopathy, dilated, 1h

TABLE 10

-107-

CODE (SEQ ID NO)	ALGOS (SEQ ID NO)	PROMOTERS (SEQ ID NO)
TMD0049 (78, 79)	CGGTTCCGACCTGTATCTCCAC (104)	AAAGAGCCTCTAAAGAAGGGTTCAGAGCTACAGGAGCTCACTGGAATA (106)
TMD0190 (80, 81)	ACCATCTGCAAACTTGGATGGC (107)	GCTTTATGTATGAAAACCCCTGTTTATCTGAGCCTAGAAGTGTCTTTGC (109)
TMD0242 (82, 83)	AAGAGCCGGAAGACAGGGAGAGG (108)	AGTCATAGTTTTAAATGGGAGGGAATTAAGTCTGCAAAATTTCCCATAT (110)
TMD0335 (84, 85)	GAGTCTCCCTGTGCGTTTGGCTG (111)	AGTCCAGCTTAAAAAGACACACACACAGAGAGAGAGACAGAG (113)
TMD0371 (86, 87)	AAGTGTAAAGCATGCCCGCCTGA (112)	TTAGTGATTTAAAAAATGTGAAGAAGAGAGTCAAGGAGTAAAGGA (114)
TMD0374 (88, 89)	GTTCCGTATGTCGCCAGGTCATC (115)	GATACAAATAATTAAAGCCAGGTTAAGGTAATATATTAAAGACCAAG (117)
TMD0469 (90, 91)	AGTCTGGCAGTCTGCGCATTTGTG (116)	ATCTCAGCAATTAAAAATGCTGAGGTGGTAAATTGTTATCAATTCTATGT (118)
TMD0719 (92, 93)	CAGGATTACGCACAAAGCGCATGG (119)	CTAGACTATTTAAAAAACCCCTGGCTTGCACAGTGGCTCAAGCCTGTAA (121)
TMD0731 (94, 95)	TGGAGGCGAGATAGCAGAGCCC (120)	AGCTGTCTCATTTAAAGTGACCTGGAGTGGATGATTTCTTGCCTAT (124)
TMD0785 (96, 97)	CTGTCCTGGGCACCCCTGATAAGC (122)	CCAATTTCTTGAAAAAGGGAGTCACTGTGGGACCATCACGCGCGGT (125)
TMD0841 (98, 99)	CCCAGGTCTGTTGCAGTGTCTC (123)	TAAACAAATACATAAATGAGGCACTTACTAGTAGTGGTAACTGCTAGGNA (128)
TMD1114 (100, 101)	CTGAGGTGTCCTCCCAAGCAGGT (126)	ACTAAATAATAAAATCAGCCAGGCTGGTGGCACATGCTGTAAATCTC (129)
TMD1148 (102, 103)	TACGCCGAGAGAGCACTGGAGATG (127)	GGGATGCATTATAAATGCAACCAAGCCAGAGGCGCCCTGGCTTCAGAACCT (130)
	GTCACCTCAGCGATCTCAACGATAGGG (131)	ATATACCTTGTTTAAAGAGGGGTATTATCACAATAAACAAGGNAAGCT (133)
	TGGAGCAGAACAGGATATAGGTGAGG (132)	ACCCTACTTTTAAAGGCTTGACAAACAGTCTAAAGTTCTCAGCTTAA (134)
	GGGTGGGAAGGAAGCAGGGAAGAG (135)	TTATTGGGCATAAAATAATGAAGAGAGGTCCACAGAGTCCCTAGGTCT (137)
	CCAGCTAGTTCATGTTGGCGCAG (136)	
	CTGTTGGGAATCTTCAGCCAGATCTCACAC (138)	AAGCAATTTGTTAAAACTGGCATTACTTTACTTCTTATGCTTTCTGTGTC (140)
	ATGAGAGTTCTGCAGCTCAGCA (139)	ACTTTAATTTTATAAAGAGGTTTACATCAAGAAATTCCAAGTGAGGTTT (141)
	GGGCCACTTCACAGACAGGAAGC (142)	AAAGCTTCTTCAAAAAAGGCGGCTTGTCTGGGCCAGAAATCAGAGTG (144)
	TGGCCTGAGAGGTAGATTCCACATAGTAGTCGT (143)	
	CTCCTTCTGTCAGAGAACAGACTGGAC (145)	CAGCGAGCGCAAAAAATGTCCCAAGATTGAGCCCTCCCACTCCCACTG (147)
	GTGATGTCGAGAAATGAGTGGGTTG (146)	TAATATRAAATATATAAATAGTGCACATTAATTTCTCTCTGTTGTT (148)
	GCAGATGACCCGACCTGACTGTTCTTC (149)	GCCAGAGAGTTTAAATGAAGCCCTACTTTTGGGGCAGGAGCGGGAGGAAC (151)
	TGGCTGTGAGTAGTCTCAGGTACCAG (150)	

TABLE 11

-108-

SEQ ID NO	GENE NUMBER	GENBANK IDENTIFIER	PREDOMINANT SITES OF EXPRESSION	OTHER SITES OF EXPRESSION	PROMOTER (SEQ ID NO)	PRIMER (FOR, REV) (SEQ ID NO)
152, 153	TMD0986	XM_061779	pancreas	low levels in testis	156-161	154,155
162, 163	TMD0987	XM_061780	pancreas	low levels in testis	166	164,165
167, 168	TMD0353	XM_061781	pancreas			169,170
171, 172	TMD0989	XM_061784	pancreas			173,174
175, 176	TMD058	XM_061785	pancreas	low levels in testis	179,180	177,178

TABLE 12

-109-

	XM_061779	XM_061780	XM_061781	XM_061784	XM_061785
outside	1-23	1-25	1-22		1-24
TM (1)	24-46	26-48	23-45		25-47
inside	47-58	49-60	46-65		48-59
TM (2)	59-78	61-83	66-88		60-82
outside	79-97	84-97	89-97		83-96
TM (3)	98-120	98-120	98-120		97-119
inside	121-140	121-139	121-140		120-139
TM (4)	141-163	140-162	141-163		140-162
outside	164-198	163-202	164-203		163-201
TM (5)	199-221	203-25	204-226		202-224
inside	222-240	226-237	227-237		225-236
TM (6)	241-260	238-260	238-260		237-259
outside	261-274	261-269	261-272		260-268
TM (7)	75-292	270-289	273-292		269-291
inside	293-314	290-318	293-323		292-311

TABLE 13

GENBANK IDENTIFIER	MOUSE HOMOLOG	061779	061780	061781	061784	061785
XM 061779			42% (63%)	36% (57%)	43% (64%)	40% (61%)
XM 061780	MOR239-6 (AY073489) 90% (93%)	42% (63%)		41% (60%)	44% (62%)	46% (67%)
XM 061781		36% (57%)	41% (60%)		43% (63%)	40% (61%)

-110-

XM_061784	MOR223 ~>85%	43% (64%)	44% (62%)	43% (63%)	81% (87%)
XM_061785	MOR223 ~>85%	40% (61%)	46% (67%)	40% (61%)	81% (87%)

TABLE 14

TABLE 15

Clone ID (Gene code)	ACCN	Predominant sites of expression	Other expression sites	Cytogenetic locus
TMD1030 (SEQ ID NO 185-186)	XM_166853	spleen	liver	11q12.2
TMD1029 (SEQ ID NO 187-188)	XM_166854	spleen, lymphocytes, liver	brain, heart, lung, lymph node	11q12.2
TMD1028 (SEQ ID NO 189-190)	XM_166855	spleen, lymphocytes	liver	11q12.2
TMD0621 (SEQ ID NO 191-192)	XM_166205	spleen	brain, heart, liver, lung and pancreas	11q12.2

TABLE 16

Clone ID	ACCN	Protein length (aa)	domain description
TMD1030	XM_166853	298	Transmembrane domain: 27 - 49 Transmembrane domain: 98 - 120 Transmembrane domain: 140 - 162 Transmembrane domain: 175 - 197 Transmembrane domain: 207 - 226

-111-

TMD1029	XM_16684	309	Transmembrane domain: 238 - 260 Transmembrane domain: 275 - 292 Transmembrane domain: 26 - 48 Transmembrane domain: 61 - 78 Transmembrane domain: 98 - 120 Transmembrane domain: 140 - 162 Transmembrane domain: 196 - 218 Transmembrane domain: 238 - 260 Transmembrane domain: 275 - 292
TMD1028	XM_166855	173	Transmembrane domain: 18 - 40 Transmembrane domain: 61 - 83 Transmembrane domain: 103 - 125 Transmembrane domain: 137 - 156
TMD0621	XM_166205	109	Transmembrane domain: 9-31 Transmembrane domain: 69 - 91

-112-

TABLE 17

CloneID	Accession	5'-3'	3'-5'
TMD1030	XM_166853	GGGATTGGTGTCACACGAAATTTCA (SEQ ID NO 197)	GAGCCTATAATATATAGCCGCTACGAGTTGGA (SEQ ID NO 198)
TMD1029	XM_166854	GTCACCTGAATTCATCTCTGGGATTGGTGC (SEQ ID NO 199)	AAACCTGTTGTACAGAGGCATTTATTGAGCC (SEQ ID NO 200)
TMD1028	XM_166855	GATATCATTTTGGGGCTGCATGATACAATTTGG (SEQ ID NO 201)	CTCCAAACCAGTGAACATCAAGTTAAATCCCAC (SEQ ID NO 202)
TMD0621	XM_166205	TTAAGCTATTAGTTAGTTTCATATGTCATGGGTTTCC (SEQ ID NO 203)	CTCATTAAACGATGGCATACATGTAAGAGAG (SEQ ID NO 204)

TABLE 18

CloneID	Accession	5'-3'	3'-5'
TMD1030	XM_166853	ATGTTCCATCTAAATGAAGCCTGAGAAACCCAGCAGTACCCACTTGTAG (SEQ ID NO 205) ACATCCATTATATAACAGGGTTAATATACCTTGTAAAGATAGCACCTAGA (SEQ ID NO 206)	
TMD1029	XM_166854	AAATGTATAAATTCCTGCATGAAATTGGGGTGGGCTTGTACTACTTTTG (SEQ ID NO 207)	
TMD1028	XM_166855	ATGTTCCATCTAAATGAAGCCTGAGAAACCCAGCAGTACCCACTTGTAG (SEQ ID NO 208) ACATCCATTATATAACAGGGTTAATATACCTTGTAAAGATAGCACCTAGA (SEQ ID NO 209)	

-113-

TND0621	XM_166205	AAATATATATTTTAAATTGGCCAGCGCGGTGGCTCAGCCCTATAATCC GGCTCAGCGCTATAATCCAGCACCTTTGGAGGCGCGGAGGTGGATCA TCCCAAATATATATATACACACACACACACACACACACATATAT CACACACATATATATACACACACATATTTTATAATCATTTAAACA (0.99) (SEQ ID NO 210) (0.97) (SEQ ID NO 211) (1.00) (SEQ ID NO 212) (0.91) (SEQ ID NO 213)
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TABLE 19

-114-

TABLE 19

(from Principles of Internal Medicine, Volume 1, Page 357, 12th Edition, McGraw-Hill Inc.)

-117-

Table 20

Clone ID	ACCN	Gene Name/Description	Predominant sites of expression	Other expression sites
TMD0077	XM_166914	Homo sapiens olfactory receptor MOR212-1 (LOC219956), mRNA.	pancreas and testis	brain, heart and kidney
TMD0233	XM_069616	Homo sapiens similar to olfactory receptor (LOC135941) mRNA	pancreas	none
TMD0256	XM_066725	Homo sapiens similar to olfactory receptor (LOC139478) mRNA	pancreas	skin and testis
TMD0258	XM_066873	Homo sapiens similar to beta-2 adrenergic receptor (LOC139760) mRNA	pancreas	colon, stomach and testis
TMD0267	XM_089550	Homo sapiens similar to CG5281 gene product (LOC159371) mRNA	pancreas and testis	adrenal gland, bone marrow, colon, heart, intestine (small), kidney, liver, pituitary, prostate, skin, stomach and thyroid
TMD0271	XM_061815	Homo sapiens similar to odorant receptor S18 gene (LOC120010) mRNA	pancreas and testis	PBL, prostate, thymus and uterus
TMD0290	XM_065813	Homo sapiens similar to unnamed protein product (LOC130644) mRNA	pancreas and testis	none
TMD0530	XM_048304	Homo sapiens hypothetical protein DKFZp564A1164 (DKFZP564A1164) mRNA	pancreas	brain, kidney, lung, lymph node, PBL, mammary gland, pituitary, stomach, testis and thyroid
TMD0574	XM_055514	Homo sapiens KIAA1910 protein (KIAA1910) mRNA	brain and pancreas	pituitary
TMD0608	XM_058332	Homo sapiens similar to putative (H. sapiens) (LOC118670) mRNA	pancreas and testis	stomach
TMD0639	XM_058690	Homo sapiens similar to data source:MGD, source key:MG196073, evidence:ISS-hexosaminidase A-putative (LOC204249), mRNA.	pancreas and testis	liver, PBL and prostate
TMD0645	XM_085376	Homo sapiens LOC146225 (LOC146225), mRNA.	pancreas and testis	bone marrow, brain, heart, kidney, liver, lung, lymph node, PBL, muscle, pituitary, prostate, skin, spleen, stomach and thymus
TMD0674	XM_059132	Homo sapiens similar to RIKEN cDNA 4930549C01 gene (LOC127309) mRNA	pancreas and testis	brain, pituitary, prostate and stomach
TMD0675	XM_059134	Homo sapiens similar to putative (H. sapiens) (LOC127348) mRNA	pancreas and testis	prostate and stomach
TMD0677	XM_059140	Homo sapiens similar to dJ39G22.2 (novel protein) (H. sapiens) (LOC127391) mRNA	pancreas and testis	prostate and stomach
TMD0726	XM_059639	Homo sapiens similar to hypothetical protein (H. sapiens) (LOC133309) mRNA	pancreas and testis	adrenal gland, brain, prostate and stomach
TMD0727	XM_059654	Homo sapiens similar to testis-specific transporter TST1 (H. sapiens) (LOC133482) mRNA	pancreas and testis	stomach
TMD0739	XM_059812	Homo sapiens similar to putative (H. sapiens) (LOC135886) mRNA	pancreas and testis	liver, lung, mammary gland, ovary, pituitary, prostate and stomach
TMD0753	XM_059954	Homo sapiens similar to putative (H. sapiens) (LOC138240) mRNA	pancreas and testis	stomach
TMD1111	NM_014386	Homo sapiens polycystic kidney disease 2-like 2 (PKD2L2) mRNA	pancreas and testis	none
TMD1127	NM_054020	Homo sapiens putative ion channel protein CATSPER2 (CATSPER2), mRNA.	pancreas and testis	none

Table 21

Clone ID	ACCN	Protein seq length (aa)	Domain description
TMD0077	XM_166914	310	7 transmembrane receptor (rhodopsin family)
			Transmembrane domains: 27 - 49
			Transmembrane domains: 61 - 83
			Transmembrane domains: 98 - 120
			Transmembrane domains: 141 - 163
			Transmembrane domains: 202 - 224
			Transmembrane domains: 237 - 259
			Transmembrane domains: 274 - 291
TMD0233	XM_069616	310	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 26 - 48
			Transmembrane domain: 60 - 77
			Transmembrane domain: 97 - 119
			Transmembrane domain: 140 - 162
			Transmembrane domain: 196 - 218
			Transmembrane domain: 239 - 261
			Transmembrane domain: 272 - 291
TMD0256	XM_066725	308	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 27 - 49
			Transmembrane domain: 61 - 83
			Transmembrane domain: 98 - 120
			Transmembrane domain: 140 - 162
			Transmembrane domain: 196 - 218
			Transmembrane domain: 239 - 258
			Transmembrane domain: 273 - 291
TMD0258	XM_066873	335	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 10 - 32
			Transmembrane domain: 39 - 61
			Transmembrane domain: 79 - 101
			Transmembrane domain: 121 - 143
			Transmembrane domain: 163 - 185
			Transmembrane domain: 226 - 248
			Transmembrane domain: 263 - 282
TMD0267	XM_089550	324	Integral membrane protein DUF6: 49-161
			Transmembrane domain: 59 - 78
			Transmembrane domain: 91 - 110
			Transmembrane domain: 115 - 137
			Transmembrane domain: 146 - 168
			Transmembrane domain: 183 - 201
			Transmembrane domain: 214 - 236
			Transmembrane domain: 246 - 265

			Transmembrane domain: 270 - 292
			Transmembrane domain: 297 - 316
TMD0271	XM_061815	291	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 29 - 51
			Transmembrane domain: 56 - 78
			Transmembrane domain: 83 - 105
			Transmembrane domain: 120 - 142
			Transmembrane domain: 163 - 185
			Transmembrane domain: 190 - 207
			Transmembrane domain: 220 - 239
			Transmembrane domain: 249 - 271
TMD0290	XM_065813	245	Transmembrane domain: 24 - 46
			Transmembrane domain: 61 - 83
			Transmembrane domain: 96 - 118
			Transmembrane domain: 128 - 150
			Transmembrane domain: 162 - 184
			Transmembrane domain: 221 - 243
TMD0530	XM_048304	708	Immunoglobulin domain: 139-206
			Immunoglobulin domain: 326-377
			Transmembrane domain: 511 - 533
TMD0574	XM_055514	696	Leucine rich repeat C-terminal domain: 212-262
			Leucine rich repeat C-terminal domain: 529-579
			Transmembrane domain: 621 - 643
TMD0608	XM_058332	105	Transmembrane domain: 13 - 35
TMD0639	XM_058690	127	Transmembrane domain: 12 - 34
			Transmembrane domain: 44 - 66
TMD0645	XM_085376	248	Transmembrane domain: 113 - 135
			Transmembrane domain: 150 - 169
			Transmembrane domain: 176 - 198
TMD0674	XM_059132	134	Transmembrane domain: 5 - 22
TMD0675	XM_059134	206	Transmembrane domain: 15 - 37
TMD0677	XM_059140	182	Transmembrane: 49 - 71
TMD0726	XM_059639	96	Transmembrane domain: 13 - 35
			Transmembrane domain: 50 - 72
TMD0727	related to XM_059654	719	Transmembrane domain: 108 - 130

			Transmembrane domain: 145 - 164
			Transmembrane domain: 171 - 193
			Transmembrane domain: 229 - 251
			Transmembrane domain: 264 - 286
			Transmembrane domain: 314 - 336
			Transmembrane domain: 421 - 443
			Transmembrane domain: 453 - 475
			Transmembrane domain: 580 - 602
			Transmembrane domain: 668 - 690
			Organic Anion Transporter Polypeptide (OATP) family, C-terminus: 125-473
			Organic Anion Transporter Polypeptide (OATP) family, N-terminus: 558-717
TMD0739	XM_059812	265	Transmembrane domain: 126 - 148
			Transmembrane domain: 185 - 207
TMD0753	XM_059954	161	Transmembrane domain: 26 - 48
TMD1111	NM_014386	609	Ion transporter domain: 284-490
			Transmembrane domain: 34 - 56
			Transmembrane domain: 274 - 296
			Transmembrane domain: 315 - 337
			Transmembrane domain: 364 - 386
			Transmembrane domain: 407 - 429
			Transmembrane domain: 469 - 491
TMD1127	NM_054020	528	Ion transporter domain: 172-340
			Transmembrane domain: 113 - 132
			Transmembrane domain: 147 - 169
			Transmembrane domain: 176 - 198
			Transmembrane domain: 241 - 263
			Transmembrane domain: 276 - 295
			Transmembrane domain: 315 - 337

Table 22

Clone ID	ACCN	Cytogenetic locus	Disease linkage
TMD0077	XM_166914	11q12.2	angioedema, hereditary; spastic paraplegia 17; osteoporosis-pseudoglioma syndrome; pancreatic tumor
TMD0233	XM_069616	7q35	glaucoma 1, open angle, f;
TMD0256	XM_066725	Xq26.1	x inactivation, familial skewed, 2; panhypopituitarism; thoracoabdominal syndrome; dandy-walker malformation with mental retardation, basal ganglia disease, and seizures; split-hand/foot malformation 2; mental retardation with optic atrophy, deafness
TMD0258	XM_066873	Xq26.1	x inactivation, familial skewed, 2; panhypopituitarism; thoracoabdominal syndrome; dandy-walker malformation with mental retardation, basal ganglia disease, and seizures; split-hand/foot malformation 2; mental retardation with optic atrophy, deafness
TMD0267	XM_089550	10q24.1	corneal dystrophy of bowman layer, type ii; alzheimer disease 6
TMD0271	XM_061815	11p15.4	charcot-marie-tooth disease, type 4b, form 2; deafness, neurosensory, autosomal recessive 18;
TMD0290	XM_065813	2p23.1	none
TMD0530	XM_048304	19q13.13	hypocalciuric hypercalcemia, familial, type iii; deafness, autosomal dominant nonsyndromic sensorineural 4; microcephaly, primary autosomal recessive, 2
TMD0574	XM_055514	13q31.1	microcoria, congenital; schizophrenia 7;
TMD0608	XM_058332	10q26.3	endometrial carcinoma
TMD0639	XM_058690	15q22.32	cataract, central saccular, with sutural opacities; obesity syndrome
TMD0645	XM_085376	16q23.1	dehydrated hereditary stomatocytosis; pancreatic acinar cancer
TMD0674	XM_059132	1p36.11	breast cancer, ductal, 2; prostate cancer/brain cancer susceptibility, melanoma, cutaneous malignant; inflammatory bowel disease 7;
TMD0675	XM_059134	1p33	carcinoma of pancreas
TMD0677	XM_059140	1p34.2	deafness, autosomal dominant nonsyndromic sensorineural 2; porphyria cutanea tarda; hypercholesterolemia, familial, ptosis, hereditary congenital 1;
TMD0726	XM_059639	10q11.22	none
TMD0727	related to XM_059654	5q21.1	anemia, dyserythropoietic congenital, type iii; dyslexia, specific, 1; colorectal cancer, hereditary nonpolyposis, type 7; cataract, central saccular, with sutural opacities
TMD0739	XM_059812	7q11.23	autism, susceptibility to, 1; muscular dystrophy, limb-girdle, type 1d; aneurysm, intracranial
TMD0753	XM_059954	9q21.12	hemophagocytic lymphohistiocytosis, familial, 1; amyotrophic lateral sclerosis with frontotemporal dementia
TMD1111	NM_014386	5q31	none
TMD1127	NM_054020	15q13-q15	nanophthalmos 2; spastic paraplegia 11, autosomal recessive; corpus callosum, agenesis of, with neuropathy; pancreatic acinar carcinoma

-122-

TABLE 23

CODE	ACCN	PRIMERS	PROMOTER
TMD0077 (SEQ ID NO 214-215)	XM_166914	TCATGGATCACCACTCCACGCTC (Forward) (SEQ ID NO 256) CACCAAGATCACCACTCCACGCA (Reverse) (SEQ ID NO 257)	GGATTGAGGCTTTTAAACCCCACTCAGTGGTGCAATGGCAGGGCTTTGA (0.88) (SEQ ID NO 258)
TMD0233 (SEQ ID NO 216-217)	XM_069616	TGCTGACGAATCTTATGAACCAAG (Forward) (SEQ ID NO 259) TCACGTCAGCCTCTCCTTCTCAGTG (Reverse) (SEQ ID NO 260)	TCACAAATCATATAAATTAGGGGAAAGAGAGAGGCGAGGTATACTCTAAAA (0.96) (SEQ ID NO 261) AATTCTCTTATTTTAAAGACCTCAGAAATGTCACCATGCTTAGTTATTTTA (0.95) (SEQ ID NO 262)
TMD0256 (SEQ ID NO 218-219)	XM_066725	GGCCATGGACAAATGTCACAGCAG (Forward) (SEQ ID NO 263) AGCAGACACATCTGGGCCATTCTAAACAC (Reverse) (SEQ ID NO 264)	GGTACTATTCTATATTTTGGGCACACAGCAATGAAGAAACAGAAAAACC (0.93) (SEQ ID NO 265) CTGGTTTCATAAAATATGGAGCAGAAAAAGTTTTTACAAATATAGAACAGCA (0.92) (SEQ ID NO 266) TAGAATGTGTATATAAAAAATGAAGCAGGGCTAGGGGAAAGAGATGGGTGA (0.91) (SEQ ID NO 267)
TMD0258 (SEQ ID NO 220-221)	XM_066873	CCTCATTTGGCTTCTCCCACTCG (Forward) (SEQ ID NO 268) GCCATCAAACTCTGAGCTGGAGATAGTGAC (Reverse) (SEQ ID NO 269)	CCAAAGAACTTTTAAAACTCCCAATGACAGTTACCAACCAAGAAATAATTA (0.97) (SEQ ID NO 270) CATCTGGAAATATA TTGCGTCCAACTCTGCACTTCTCTCTATTCCTT (0.96) (SEQ ID NO 271) CTGGGCCCCCTCAAAAAAGCTCACTTCCCTCACTTCCCACTTCAACTGAT (0.91) (SEQ ID NO 272)
TMD0267 (SEQ ID NO 222-223)	XM_089550	TGGCCTCGTTGAAAGTGTCATCATCC (Forward) (SEQ ID NO 273) TTGGTACCAATTTACGAA TGGCCGC (Reverse) (SEQ ID NO 274)	AAACGGCA TTTTAAAAATGCAGGTTTAAA TTGTTATCCTCATCTATGGTT (0.98) (SEQ ID NO 275)
TMD0271 (SEQ ID NO 224-225)	XM_061815	CTGGACTTGAGCAGTACCAGCTCTGGATC (Forward) (SEQ ID NO 276) CATATTTCCACAGCAATTTTGACAAATGG (Reverse) (SEQ ID NO 277)	ATTTTGTTATATATAGAGGAGTCTAGGAAAGAGACTCGTGGTCTGATTC (0.97) (SEQ ID NO 278) TACTCATATTTTATATAGCAGCAACTTACATTGACCCAGGAGAACTCAGT (0.94) (SEQ ID NO 279)
TMD0290 (SEQ ID NO 226-227)	XM_065813	GTTACCCACCCAAACCGTCACGACC (Forward) (SEQ ID NO 280) CAGGCGATGCCAGAGAAAGACGATG (Reverse) (SEQ ID NO 281)	CTAGAA TTTACATATAAAAGGAGCTGGAGGAGCTTTTGCAGCAACTTTGCAT (0.97) (SEQ ID NO 282) TTTTCTCTTTTAAAAACACGCTTTTCACTCTCAAAACAGCAGAGAAATGAA (0.98) (SEQ ID NO 283) AACTGGGTCTATAAGAGAGCCAGGGCACTTATTCATCCAAAGGGCAGATG (0.99) (SEQ ID NO 284)
TMD0330 (SEQ ID NO 228-229)	XM_048304	CTATGACTTCAAGCCCACTGGGCA (Forward) (SEQ ID NO 285) AAGTCCGCAACTTTGCTCCTGGCTC (Reverse) (SEQ ID NO 286)	GGGCGGGAGTAAAAAGGCAGAGTCCAA TTTCCACGGCCCCCAGTGTGGGTG (0.86) (SEQ ID NO 287)

-123-

CODE	ACCN	PRIMERS	PROMOTER
TMD0374 (SEQ ID NO 230-231)	XM_055514	TCAATGCCATGCCCAACTGAGGA (Forward) (SEQ ID NO 288) CAACACCGAGATGGACACCCCTGCT (Reverse) (SEQ ID NO 289)	CTTTAAGGTTAAAAATGTGGGTTTATAGATGATGTCCTTTCTAAACAGC (0.99) (SEQ ID NO 290) TCAGGATGCTCTAAAAAAGATCTCTCTAGTGTACACACGTGCACACACACA (0.97) (SEQ ID NO 291) AGTAACTCTATTTTAAAAAGACCTAAAAATTTCAAAATGCTAAAAATGATCTAT (0.90) (SEQ ID NO 292) AATAAATGTTTTTAAAAAGCACCTCTCTTCCGAATGGTGGAGCTGGTGGGGC (0.91) (SEQ ID NO 293)
TMD0608 (SEQ ID NO 232-233)	XM_058332	CTCAGGACGAAGTCAATGTCGGCATC (Forward) (SEQ ID NO 294) GAAGATTTTGTGCCCAAGCTTTCCCAAG (Reverse) (SEQ ID NO 295)	TATCTCACCTTAAAGTGGGAGCTAAGCCATGAGGGACCAAGGCATAAG (0.99) (SEQ ID NO 296) TTACATATGTATACATGTGCCATGCTGTGCTGCTGCACCCCATTAACCTCGT (0.96) (SEQ ID NO 297)
TMD0639 (SEQ ID NO 234-235)	XM_058690	TCCATGCTCAGCTTCATCTCAGCTACC (Forward) (SEQ ID NO 298) TCCATCTCAGACCTTGGCCCTTCA (Reverse) (SEQ ID NO 299)	AAATAACCCCATTAATAAAGTGGGCAAAAGGCGCATGAACACTTTTCAAAAGA (1.00) (SEQ ID NO 300)
TMD0645 (SEQ ID NO 236-237)	XM_085376	AGGACGGTAAGGAGCCATCGGACA (Forward) (SEQ ID NO 301) CTTGCCAGGTTCTGTGGCTTGG (Reverse) (SEQ ID NO 302)	TCCTTTGTCTATAAATAGGACTTTTGAATTTTCTGGACTAGAGAAATTGTAT (0.94) (SEQ ID NO 303)
TMD0674 (SEQ ID NO 238-239)	XM_059132	ACGACTCCAAAGAACAGCAAGGCCG (Forward) (SEQ ID NO 304) AAGGTAACATCGGCAGAGGCCAGC (Reverse) (SEQ ID NO 305)	GCTAGCATTTTTTAAAGCTGATGTCTTCACTGGGCAACGGGGACTCACAC (0.94) (SEQ ID NO 306)
TMD0675 (SEQ ID NO 240-241)	XM_059134	CGGCCAGGTACCAAAAGCTCAGCTG (Forward) (SEQ ID NO 307) GCCAGATTCAGGAGGGAAATGGAAAGAGAAC (Reverse) (SEQ ID NO 308)	TGATCTACTTTTTTAAAAAGGATCATGCTGGCTGCTGGTGGGATTTAGGATA (0.91) (SEQ ID NO 309) TGATAGTGATAAAAAAAGTGGCCAGATTTTGGTTATATTTTGAATAAAA (0.99) (SEQ ID NO 310) TATAGTGATATTTAAAGCCAGGGTCTGGTGAGATAAACTGATGGAATGA (0.93) (SEQ ID NO 311) ATTGGAGGAGCTATAAAGAGGGGAGTCATTAATAATGGTCTAAGAAAGCTGA (0.96) (SEQ ID NO 312) AGAGGGGAGTCAATTAATAATGGTCTAAGAAAGCTGAGCTACAAAGCAGTGGT (0.97) (SEQ ID NO 313) GACATTCACCCCAAAAAATGCCACTGGATGAAGTCCCTCTCTCCATTAA (0.92) (SEQ ID NO 314)

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CODE	ACCN	PRIMERS	PROMOTER
TMD0677 (SEQ ID NO 242-243)	XM_059140	TTGGGAGAGACTAGTGCACCTCAGCA (Forward) (SEQ ID NO 315) GAGCAATCCCTCTTCGTGGCAGGT (Reverse) (SEQ ID NO 316)	AAAAGTGCCTTTAAACAGGGGGGTGGAGGGGCTTATGAGAAAGGGACCA (1.00) (SEQ ID NO 317) CCAATTTCTACTAAAAATGACAGATGACCCAGGGGTGGCAGCTGCCTGTA (0.95) (SEQ ID NO 318) AAAAAATTTTAAAAAAGCCCTGTTTATATCTCTACCTCTTCTGGGTGC (0.98) (SEQ ID NO 319) AAAAAATTTTAAAAATCCCATCTCTCTCACTTTCCAATTCACCTCAAT (0.93) (SEQ ID NO 320)
TMD0726 (SEQ ID NO 244-245)	XM_059639	ACTTCCAAACATCTCAACCTCTCAGAGTCTCATTT (Forward) (SEQ ID NO 321) TGCAGCACCATCATGTAAAGGACAA (Reverse) (SEQ ID NO 322)	TTTTTAACTATAAAAAAGTGGGATCAGAAAAACACAGTCATAAAGGGAAA (0.97) (SEQ ID NO 323) GTATATGCTATATATCAGGATTCACCTTTAAATGGCATTGAGTTCCAGGA (0.98) (SEQ ID NO 324) ATAACAAATTTAAAAATTAGCCACCATGGTGGTACACACCTGTCTGTTCT (0.99) (SEQ ID NO 325) AAAAAGTGAAAAAAGGTGAGGGAGACTTTAACTTTCTGAAATATATT (0.92) (SEQ ID NO 326)
TMD0727 (SEQ ID NO 246-247)	XM_059634 (related to)	CCAGAAAGCCGGGAGAAAGTGGATG (Forward) (SEQ ID NO 327) TGACAGAGCTAGGCATATGAGCACTGGA (Reverse) (SEQ ID NO 328)	CTAAAGAGCTTATATACGCTAAAGAAAAAAGAAACCAATAAGAAAGTTGC (0.96) (SEQ ID NO 329)
TMD0739 (SEQ ID NO 248-249)	XM_059812	GCAGTTGGTTCAGAAACGAGATCACC (Forward) (SEQ ID NO 330) GGCAGATGGGATACATTTATCTCTGGG (Reverse) (SEQ ID NO 331)	ACTAAAAATACAAAAAAGTAGCCGGGTATGGTGGTAGGGCGCTATAATCC (0.93) (SEQ ID NO 332) GGTAGGGCGCTATAATCCAGCTACTTGGGAGGCTGAGGCAGGAGAAATG (0.92) (SEQ ID NO 333)
TMD0753 (SEQ ID NO 250-251)	XM_059934	TCGGCTTGGAAATCAGAAATGAGAAAG (Forward) (SEQ ID NO 334) TGCACAAAGAAATGATTGCAGCAGTGAGTAG (Reverse) (SEQ ID NO 335)	AAAAGCTTATATAAAAAAGGTTTGTGTTGTTGTTGAGACGGAGTT (0.97) (SEQ ID NO 336) GGCCAACTTATATAAAAGTTTATGTTTTGTTCTGTATAATTCGTTTCT (0.91) (SEQ ID NO 337) AAGTTAAGTTTAAAAAAGAACAGGCTACAAAGTTATAGCTATGGGTGAT (0.96) (SEQ ID NO 338)
TMD1111 (SEQ ID NO 252-253)	NM_014386	GGGCGGTGTAGTGCAGGTCGG (Forward) (SEQ ID NO 339) CCTCCAGTTGCAGGGAATTCCTGCC (Reverse) (SEQ ID NO 340)	AATCAAAATATTTAAACGGGACTGTCTCTCTCTCACAAGTCTAGATCT (0.92) (SEQ ID NO 341)
TMD1127 (SEQ ID NO 254-255)	NM_054020	GCGTGTGAGCAGGCTTCATGTGC (Forward) (SEQ ID NO 342) CTCCTCTGGATGATCTGCCCTTG (Reverse) (SEQ ID NO 343)	ATTGGGTGCATATATTTAGGATAGTTAGCTCTCTCTCTTGTGAAATGATC (0.89) (SEQ ID NO 344)

CLAIMS:

1. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), or TMD0890 (XM_060959) of claim 28, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization.

2. A method of claim 1, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

3. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), or TMD0890 (XM_060959) of claim 28, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding.

4. A method of claim 3, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

5. A method of delivering an agent to an immune cell, comprising:

contacting an immune cell with an agent coupled to binding partner specific for a polypeptide coded for by TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), or TMD0890 (XM_060959) of claim 28, whereby said agent is delivered to said cell.

6. A method of claim 5, wherein the agent is a therapeutic agent or an imaging agent.

7. A method of claim 5, wherein the agent is cytotoxic.

8. A method of claim 5, wherein the binding partner is an antibody.

5

9. A method of modulating the maturation of an immune system cell, comprising:

contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28, whereby the maturation of an immune cell is modulated.

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10. A method of modulating interactions between lymphoid and non-lymphoid immune system cells, comprising:

contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28, whereby the interaction is modulated.

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11. A method of expressing a heterologous polynucleotide in immune system cells, comprising:

expressing a nucleic acid construct in immune system cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected from SEQ ID NOS 5, 10, 11, 16-19, 29-32, 37-39, 44-46, 51-54, and 59-62.

25

12. A method of treating an immune system disease, comprising:

administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025

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-128-

(XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28.

13. A method of claim 12, wherein said agent is an antibody or an antisense which is effective to inhibit translation of said gene.

14. A method of diagnosing an immune disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:

assessing the expression of a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28 in a tissue sample comprising immune system cells.

15. A method of claim 14, wherein assessing is:

measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

16. A method of claim 14, wherein said assessing detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28, or a polynucleotide probe having 95% sequence identity or more to a sequence set forth in SEQ ID NOS 1, 6, 12, 20, 25, 33, 40, 47, or 55, effective specific fragments thereof, or complements thereto.

17. A method of assessing a therapeutic or preventative intervention in a subject having an

immune system disease, comprising,

determining the expression levels of a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28 in a tissue sample comprising immune system cells.

18. A method of claim 17, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

19. A method for identifying an agent that modulates the expression of a gene or polypeptide in the immune system gene complex, comprising,

contacting an immune system cell with a test agent under conditions effective for said test agent to modulate the expression of a gene selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28, or the biological activity of a polypeptide encoded thereby, in said immune system cell, and determining whether said test agent modulates said gene or polypeptide.

20. A method of claim 19, wherein said agent is an antisense polynucleotide which is effective to inhibit translation of said gene or an antibody specific for said polypeptide.

21. A method of detecting polymorphisms in a gene in the immune system gene complex, comprising: comparing the structure of:

genomic DNA or RNA or cDNA or a polypeptide comprising all or part of a gene selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28 with the structure of SEQ ID NOS 1, 6, 12, 20, 25, 33, 40, 47, or 55.

22. A method of claim 20, wherein said polymorphism is a nucleotide deletion, substitution, inversion, or transposition.

5 23. A method of identifying a genetic basis for an immune disease or disease-susceptibility, comprising:

determining the association of an immune disease or disease-susceptibility with a nucleotide sequence present in a genome comprising the gene complex of claim 28.

10 24. A method of claim 23, wherein determining is performed by producing a human-linkage map of said complex.

25. A method of claim 23, wherein determining is performed by comparing the nucleotide sequences between normal subjects and subjects having an immune system disease.

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26. A non-human, transgenic mammal, or a cell thereof, whose genome comprises a functional disruption of a gene selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888

20 (XM_060957), and TMD0890 (XM_060959) of claim 28, or a mouse homolog thereof, and which has a defect in immune system function.

27. A method of selecting a gene predominantly expressed in immune system cells from a database comprising polynucleotide sequences for genes, comprising:

-131-

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for a gene selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890

5 (XM_060959), or complements to the polynucleotides sequence,

wherein said displayed sequences have been retrieved from said database upon selection by a user.

28. A composition consisting essentially of the 1q22 immune gene complex, comprising
10 TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) genes, or a fragment thereof comprising at least two said genes.

15 29. A composition of claim 28, wherein said complex consists essentially of the chromosome region between STS markers SHGC-81033 and SHGC-145403, or a fragment thereof comprising at least two said genes.

30. A composition of claim 28, wherein said complex consists essentially of the
20 chromosome region between STS markers SHGC-81033 and DIS3249, G15944, GDB:191077, or GDB:196442, or a fragment thereof comprising at least two said genes.

31. A composition of claim 28, wherein said complex consists essentially of the
25 chromosome region between STS markers RH118729 and DIS2577 or SHGC-145403, or a fragment thereof comprising at least two said genes.

32. A method of detecting an immune system cell, comprising:
contacting a sample comprising cells with a polynucleotide specific for a XM_062147 (SEQ ID NO 63) or XM_061676 (SEQ ID NO 69) of claim 59 under conditions effective for
30 said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization.

-132-

33. A method of claim 32, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

5 34. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for XM_062147 (SEQ ID NO 64) or XM_061676 (SEQ ID NO 70) of claim 59 under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding.

10

35. A method of claim 34, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

36. A method of delivering an agent to an immune cell, comprising:

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contacting an immune cell with an agent coupled to binding partner specific for XM_062147 (SEQ ID NO 64) or XM_061676 (SEQ ID NO 70) of claim 59, whereby said agent is delivered to said cell.

37. A method of claim 36, wherein the agent is a therapeutic agent or an imaging agent.

20

38. A method of claim 36, wherein the agent is cytotoxic.

39. A method of claim 36, wherein the binding partner is an antibody.

25 40. A method of modulating the maturation of an immune system cell, comprising:

contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59, whereby the maturation of an immune cell is modulated.

30 41. A method of modulating interactions between lymphoid and non-lymphoid immune system cells, comprising:

contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59, whereby the interaction is modulated.

- 5 42. A method of expressing a heterologous polynucleotide in immune system cells, comprising:

expressing a nucleic acid construct in immune system cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is SEQ ID NOS 65, 66, 72, 73, 74, or 75.

10

43. A method of treating an immune system disease, comprising:

administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59.

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44. A method of claim 43, wherein said agent is an antibody or an antisense which is effective to inhibit translation of said gene.

- 20 45. A method of diagnosing an immune disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:

assessing the expression of a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59 in a tissue sample comprising immune system cells.

- 25 46. A method of claim 45, wherein assessing is:

measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

- 30 47. A method of claim 45, wherein said assessing detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,

-134-

RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from SEQ ID NOS 67, 68, 76, and 77.

- 5 48. A method of assessing a therapeutic or preventative intervention in a subject having an immune system disease, comprising,
- determining the expression levels of a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59 in a tissue sample comprising immune system cells.

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49. A method of claim 48, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

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50. A method for identifying an agent that modulates the expression of a gene or polypeptide in the immune system gene complex, comprising,

contacting an immune system cell with a test agent under conditions effective for said test agent to modulate the expression of XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59, or a polypeptide encoded thereby, in said immune system cell, and

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determining whether said test agent modulates said gene.

51. A method of claim 50, wherein said agent is an antisense polynucleotide to a target polynucleotide sequence selected from SEQ ID NOS 63 or 69 and which is effective to inhibit translation of said gene.

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52. A method of detecting polymorphisms in a gene in the immune system gene complex, comprising:

comparing the structure of: genomic DNA or RNA or cDNA comprising all or part of an allele of XM_062147 or XM_061676 with SEQ ID NOS 63 or 69 of claim 59.

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53. A method of claim 52, wherein said polymorphism is a nucleotide deletion, substitution,

inversion, or transposition.

54. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by XM_062147 (SEQ ID NO 63) or XM_061676 (SEQ ID NO 69) of claim 59, and which has a defect in immune system function.

55. A mammalian immune system cell whose genome comprises a functional disruption of a gene represented by XM_062147 (SEQ ID NO 63) or XM_061676 (SEQ ID NO 69) of claim 59, and which has a defect in immune system function.

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56. A mammalian cell of claim 55, wherein said cell is a mouse cell.

57. A non-human, transgenic mammal, or a cell thereof, comprising a gene operatively linked to an expression control sequence effective to express said gene in immune system, wherein said sequence is SEQ ID NOS 65, 66, 71, 72, 73, 74, or 75.

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58. A method of selecting a gene predominantly expressed in immune system cells from a database comprising polynucleotide sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59, or complements to the polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

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25 59. A composition comprising:

bone marrow specific genes consisting essentially of XM_062147 (SEQ ID NO 63 or 64) and XM_061676 (SEQ ID NO 69 or 70), or polypeptides thereof.

60. A method of detecting a kidney cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for a polynucleotide, or a naturally-occurring polymorphisms thereof, of claim 81 under conditions effective for said polynucleotide to hybridize specifically to said gene, and

30

detecting specific hybridization.

61. A method of claim 60, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,

5 RACE PCR, or *in situ* hybridization.

62. A method of detecting an kidney cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide

coded for by a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof,

10 under conditions effective for said binding partner bind specifically to said polypeptide, and
detecting specific binding.

63. A method of claim 62, wherein said detecting is performed by: immunocytochemistry,
immunoprecipitation, or Western blot.

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64. A method of delivering an agent to a kidney cell, comprising:

contacting a kidney cell with an agent coupled to binding partner specific for

polypeptide coded for by a polynucleotide of claim 81, or a naturally-occurring

polymorphism thereof, whereby said agent is delivered to said cell.

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65. A method of claim 64, wherein the agent is a therapeutic agent, a cytotoxic agent, or an
imaging agent.

66. A method of claim 64, wherein the binding partner is an antibody.

25

67. A method of modulating a kidney cell, comprising:

contacting said cell with an agent effective to modulate a polynucleotide, or

polypeptide encoded thereby, or a naturally-occurring polymorphism thereof, of claim 81,
whereby the kidney cell is modulated.

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68. A method of assessing kidney function, comprising:

-137-

detecting a polypeptide coded for by a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of kidney function.

5 69. A method of claim 68, wherein said detecting is performed using an antibody which is specific for said polypeptide.

70. A method of claim 69, wherein said detecting is performed by RIA, ELISA, or Western blot.

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71. A method of expressing a heterologous polynucleotide in kidney cells, comprising:
expressing a nucleic acid construct in kidney cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected from SEQ ID NOS. 106, 109, 110, 113, 114, 117, 118, 121,
15 124, 125, 128-130, 133, 134, 137, 140, 141, 144, 147, 148, and 151.

72. A method of diagnosing a kidney disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:

20 assessing the expression of a polynucleotide of claim 81, or a polypeptide encoded thereby, or naturally-occurring polymorphisms thereof, in a tissue sample comprising kidney cells.

73. A method of claim 72, wherein assessing is:

25 measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

74. A method of assessing a therapeutic or preventative intervention in a subject having a kidney disease, comprising,

30 determining the expression levels of a polynucleotide of claim 81, a naturally-occurring polymorphism thereof, or polypeptide encoded thereby, in a tissue sample

comprising kidney cells.

75. A method of claim 74, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

5

76. A method for identifying an agent that modulates the expression of a polynucleotide or polypeptide selectively expressed in kidney cells, comprising,

contacting an kidney cell with a test agent under conditions effective for said test agent to modulate the expression of a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof, or the biological activity of a polypeptide encoded thereby, in said kidney cell, and

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determining whether said test agent modulates said gene or polypeptide.

77. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by a polynucleotide of claim 81, or a homolog thereof, and which has a defect in kidney function.

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78. A mammalian kidney cell whose genome comprises a functional disruption of a gene represented by a polynucleotide of claim 81, or a homolog thereof, and which has a defect in kidney function.

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79. A mammalian cell of claim 78, wherein said cell is a mouse cell.

80. A method of selecting a gene predominantly expressed in kidney cells from a database comprising polynucleotide sequences for genes, comprising:

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displaying, in a computer-readable medium, a polynucleotide sequence, or a polypeptide encoded thereby, of claim 81, or complements to the polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

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81. A composition comprising two or more of the following polynucleotides expressed selectively in kidney:

TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108).

82. A method of detecting a pancreas cell, comprising:
contacting a sample comprising cells with a polynucleotide specific for TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, of claim 113 under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization.

83. A method of claim 82, wherein said detecting is performed by:
Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

84. A method of detecting a pancreas cell, comprising:
contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, of claim 113 under conditions effective for said binding partner bind specifically to said polypeptide, and, detecting specific binding.

85. A method of claim 84, wherein said detecting is performed by:
immunocytochemistry, immunoprecipitation, or Western blot.

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86. A method of delivering an agent to a pancreas cell, comprising:
contacting a pancreas cell with an agent coupled to binding partner specific for

TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, of claim 113, whereby said agent is delivered to said cell.

87. A method of claim 86, wherein the agent is a therapeutic agent or an imaging agent.

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88. A method of claim 86, wherein the agent is cytotoxic.

89. A method of claim 86, wherein the binding partner is an antibody.

10 90. A method of modulating a pancreas cell, comprising:

contacting said cell with an agent effective to modulate TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or the biological activity of a polypeptide encoded thereby, of claim 113, whereby the pancreas cell is modulated.

15 91. A method of assessing pancreas function, comprising:

detecting a polypeptide coded for TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of pancreas function.

20 92. A method of claim 91, wherein said detecting is performed using an antibody which is specific for said polypeptide.

93. A method of claim 91, wherein said detecting is performed by RIA, ELISA, or Western blot.

25

94. A method of expressing a heterologous polynucleotide in pancreas cells, comprising:

expressing a nucleic acid construct in pancreas cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is SEQ ID NOS 156-161, 166, 179, or 180.

30

95. A method of diagnosing a pancreas disease associated with abnormal gene expression,

or determining a subject's susceptibility to such disease, comprising:

assessing the expression of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or polypeptide encoded thereby, of claim 113 in a tissue sample comprising pancreas cells.

5

96. A method of claim 95, wherein assessing is:

measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

10

97. A method of claim 95, wherein said assessing is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from SEQ ID NOS 154, 155, 164, 165, 169, 170, 173, 174, 177, 178, or a complement thereto.

15

98. A method of assessing a therapeutic or preventative intervention in a subject having a pancreas disease, comprising,

determining the expression levels of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or a polypeptide encoded thereby, of claim 113 in a tissue sample comprising pancreas cells.

20

99. A method of claim 98, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

25

100. A method for identifying an agent that modulates the expression of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or the biological activity of a polypeptide encoded thereby, comprising,

contacting a pancreas cell with a test agent under conditions effective for said test agent to modulate the expression of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785 of claim 113, or the biological activity of a polypeptide encoded thereby, in said

30

-142-

pancreas cell, and

determining whether said test agent modulates said gene or polypeptide.

101. A method of claim 100, wherein said agent is an antisense polynucleotide to a target
5 polynucleotide sequence selected from SEQ ID NO 152, 162, 167, 171, or 175 and which is
effective to inhibit translation of said gene.

102. A method of detecting polymorphisms in TMD0986, XM_061780, XM_061781,
XM_061784, or XM_061785, comprising,

10 comparing the structure of: genomic DNA or RNA or cDNA comprising all or part
of an allele of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785,
with SEQ ID NOS 152, 153, 162, 163, 167, 168, 171, 172, 175, or 176 of claim 113.

103. A method of claim 102, wherein said polymorphism is a nucleotide deletion,
15 substitution, inversion, or transposition.

104. A method of identifying a pancreatic disease or pancreatic disease-susceptibility,
comprising:

determining the association of a pancreatic disease or pancreatic disease-susceptibility
20 with a nucleotide sequence present within the pancreatic gene complex of claim 113.

105. A method of claim 104, wherein the pancreatic gene complex is from LOC160025-
LOC119954.

106. A method of claim 104, wherein determining is performed by producing a human-
25 linkage map of said complex.

107. A method of claim 104, wherein determining is performed by comparing the
nucleotide sequences between normal subjects and subjects having a pancreas disorder.

30 108. A non-human, transgenic mammal whose genome comprises a functional disruption of
a gene represented by TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785

-143-

of claim 113, and which has a defect in pancreas function.

109. A mammalian pancreas cell whose genome comprises a functional disruption of a gene represented by TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785 of claim

5 113, and which has a defect in pancreas function.

110. A mammalian cell of claim 109, wherein said cell is a mouse cell.

111. A pancreas cell, comprising a gene operatively linked to an expression control sequence
10 effective to express said gene in pancreas, wherein said sequence is SEQ ID NOS 156-161,
179, or 180.

112. A method of selecting a gene predominantly expressed in pancreas cells from a database comprising polynucleotide sequences for genes, comprising:

15 displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785 of claim 113, or complements to the polynucleotides sequence,

wherein said displayed sequences have been retrieved from said database upon selection by a user.

20

113. A composition comprising: a pancreas specific gene consisting essentially of TMD0986, XM_061780, XM_061781, XM_061784, and/or XM_061785, or a polypeptide encoded thereby.

25 114. An isolated polynucleotide comprising a polynucleotide sequence which codes without interruption for a human TMD0986 having an amino acid sequence set forth in SEQ ID NO 153, or a complement thereto.

115. An isolated polynucleotide comprising,

30 a human TMD0986 polynucleotide sequence having 90% or more nucleotide sequence identity to the polynucleotide sequence set forth in SEQ ID NO 152 along its entire

-144-

length, which codes without interruption for human TMD0986, or a complement thereto, and which has G-protein coupling activity.

116. An isolated human TMD0986 polypeptide comprising the amino acid sequence of a
5 human TMD0986 as set forth in SEQ ID NO 153.

117. An isolated human TMD0986 polypeptide consisting essentially of amino acids 1-117 of a human TMD0986 as set forth in SEQ ID NO 153.

10 118. An isolated polypeptide which is human TMD0986 having 90% or more amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO 153, and which has protein binding activity.

119. An antibody specific for an epitope selected from the polypeptide of claim 117.
15

120. A method of detecting an retinal cell, comprising:
contacting a sample comprising cells with a polynucleotide specific for NM_013941
(SEQ ID NO 181), or a naturally-occurring polymorphisms thereof, of claim 142 under
conditions effective for said polynucleotide to hybridize specifically to said gene, and
20 detecting specific hybridization.

121. A method of claim 120, wherein said detecting is performed by:
Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,
RACE PCR, or *in situ* hybridization.
25

122. A method of detecting an retinal cell, comprising:
contacting a sample comprising cells with a binding partner specific for a polypeptide
coded for by NM_013941 (SEQ ID NO 182), or a naturally-occurring polymorphism thereof,
of claim 142 under conditions effective for said binding partner bind specifically to said
30 polypeptide, and
detecting specific binding.

-145-

123. A method of claim 122, wherein said detecting is performed by:
immunocytochemistry, immunoprecipitation, or Western blot.

124. A method of delivering an agent to a retinal cell, comprising:

5 contacting a retinal cell with an agent coupled to binding partner specific for by
NM_013941 (SEQ ID NO 182), or naturally-occurring polymorphism thereof, of claim 142,
whereby said agent is delivered to said cell.

125. A method of claim 124, wherein the agent is a therapeutic agent or an imaging agent.

10

126. A method of claim 124, wherein the agent is cytotoxic.

127. A method of claim 124, wherein the binding partner is an antibody.

15 128. A method of modulating a retinal cell, comprising:

 contacting said cell with an agent effective to modulate NM_013941 (SEQ ID NO
181 or 182), or the biological activity of a polypeptide encoded thereby, of claim 142,
whereby the retinal cell is modulated.

20 129. A method of diagnosing a retinal disease associated with abnormal gene expression, or
determining a subject's susceptibility to such disease, comprising:

 assessing the expression of NM_013941, a polymorphism thereof, or polypeptide
encoded thereby, of claim 142 in a tissue sample comprising retinal cells.

25 130. A method of claim 129, wherein assessing is:

 measuring expression levels of said gene, determining the genomic structure of said
gene, determining the mRNA structure of transcripts from said gene, or measuring the
expression levels of polypeptide coded for by said gene.

30 131. A method of claim 129, wherein said assessing detecting is performed by:

 Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,

-146-

RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from SEQ ID NOS 183 or 184, or a complement thereto.

5 132. A method of assessing a therapeutic or preventative intervention in a subject having an retinal disease, comprising,

determining the expression levels of NM_013941, a polymorphism thereof, or polypeptide encoded thereby, of claim 142 in a tissue sample comprising retinal cells.

10 133. A method of claim 132, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

134. A method for identifying an agent that modulates the expression of NM_013941 or the biological activity of a polypeptide encoded thereby, comprising,

15 contacting an retinal cell with a test agent under conditions effective for said test agent to modulate the expression of NM_013941 or a polymorphism thereof, of claim 142, or the biological activity of a polypeptide encoded thereby, in said retinal cell, and determining whether said test agent modulates said gene or polypeptide.

20 135. A method of claim 134, wherein said agent is an antisense polynucleotide to a target polynucleotide sequence selected from SEQ ID NO 181 and which is effective to inhibit translation of said gene.

25 136. A method of detecting polymorphisms in NM_013941, comprising:
comparing the structure of: genomic DNA or RNA or cDNA comprising all or part of an allele of NM_013941, with SEQ ID NOS 181 or 182 of claim 142.

137. A method of claim 136, wherein said polymorphism is a nucleotide deletion, substitution, inversion, or transposition.

30 138. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by NM_013941 (SEQ ID NO 181) of claim 142, and which has a defect in

retinal function.

139. A mammalian retinal cell whose genome comprises a functional disruption of a gene represented by NM_013941 (SEQ ID NO 181) of claim 142, and which has a defect in retinal
5 function.

140. A mammalian cell of claim 139, wherein said cell is a mouse cell.

141. A method of selecting a gene predominantly expressed in retinal cells from a database
10 comprising polynucleotide sequences for genes, comprising:
displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide
sequence for NM_013941 (SEQ ID NO 181 or 182) of claim 142, or complements to the
polynucleotides sequence,
wherein said displayed sequences have been retrieved from said database upon
15 selection by a user.

142. A composition comprising:
a retinal specific gene consisting essentially of NM_013941 (SEQ ID NO 181 or
182), or a polypeptide encoded thereby.

20

143. A method of detecting a spleen cell, comprising:
contacting a sample comprising cells with a polynucleotide specific for TMD1030
(XM_166853) or TMD0621 (XM_166205) of claim 170 under conditions effective for said
polynucleotide to hybridize specifically to said gene, and
25 detecting specific hybridization.

144. A method of claim 143, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,
RACE PCR, or *in situ* hybridization.

30

145. A method of detecting a spleen cell, comprising:
contacting a sample comprising cells with a binding partner specific for a polypeptide

-148-

coded for by TMD1030 (XM_166853) or TMD0621 (XM_166205) of claim 170 under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding.

5 146. A method of claim 145, wherein said detecting is performed by:
immunocytochemistry, immunoprecipitation, or Western blot.

147. A method of delivering an agent to a spleen cell, comprising:
contacting a spleen with an agent coupled to binding partner specific for TMD1030
10 (XM_166853) or TMD0621 (XM_166205) of claim 170, whereby said agent is delivered to
said cell.

148. A method of claim 147, wherein the agent is a therapeutic agent or an imaging agent.

15 149. A method of claim 148, wherein the agent is cytotoxic.

150. A method of claim 147, wherein the binding partner is an antibody.

151. A method of modulating a spleen, immune, or reticuloendothelial cell, comprising:
20 contacting said cell with an agent effective to modulate TMD1030 (XM_166853),
TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), or the
biological activity of a polypeptide encoded thereby, of claim 170, whereby the cell is
modulated.

25 152. A method of assessing spleen function, comprising:
detecting a polypeptide coded for by TMD1030 (XM_166853) or TMD0621
(XM_166205) of claim 170, or fragments thereof, in a body fluid, whereby the amount of
said polypeptide in said fluid is a measure of spleen function.

30 153. A method of claim 152, wherein said detecting is performed using an antibody which is
specific for said polypeptide.

154. A method of claim 152, wherein said detecting is performed by RIA, ELISA, or Western blot.

5 155. A method of expressing a heterologous polynucleotide in spleen cells, comprising:
expressing a nucleic acid construct in spleen cell, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is SEQ ID NO 205-213.

10 156. A method of assessing a therapeutic or preventative intervention in a subject having a spleen or lymphoid disease, comprising,
determining the expression levels of TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), or a polypeptide encoded thereby, of claim 170 in a tissue sample comprising spleen, lymphoid, or
15 reticuloendothelial cells.

157. A method of claim 156, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

20 158. A method for identifying an agent that modulates the expression of TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), comprising,
contacting a spleen, lymphoid, or reticuloendothelial cell, with a test agent under conditions effective for said test agent to modulate the expression of TMD1030
25 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), of claim 170, and
determining whether said test agent modulates said gene.

30 159. A method of claim 158, wherein said agent is an antisense which is effective to inhibit translation of said gene.

160. A method for identifying an agent that modulates the expression of a polypeptide coded for by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), comprising,

contacting a polypeptide coded for by TMD1030 (XM_166853), TMD1029

5 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205) of claim 170, with a test agent under conditions effective for said test agent to modulate said polypeptide, and determining whether said test agent modulates said polypeptide.

161. A method of detecting polymorphisms in comprising, comparing the structure of :

10 genomic DNA or RNA or cDNA comprising all or part of an allele of TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), with SEQ ID NOS 185, 187, 189, or 191 of claim 170.

162. A method of claim 161, wherein said polymorphism is a nucleotide deletion,

15 substitution, inversion, or transposition.

163. A method of identifying a genetic basis for a spleen, lymphoid, and/or reticuloendothelial disease or disease-susceptibility, comprising: determining the association of a spleen, lymphoid, and/or reticuloendothelial disease or disease-susceptibility with a

20 nucleotide sequence present in the gene complex of claim 170.

164. A method of claim 163, wherein determining is performed by producing a human-linkage map of said complex.

25 165. A method of claim 163, wherein determining is performed by comparing the nucleotide sequences between normal subjects and subjects having a spleen, lymphoid, and/or reticuloendothelial disease.

166. A non-human, transgenic mammal, or a cell thereof, whose genome comprises a
30 functional disruption of a gene represented by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205) of claim 170, and

which has a defect in spleen, lymphoid, and/or reticuloendothelial disease function.

167. A mammalian cell of claim 166, wherein said cell is a mouse cell.

5 168. A spleen, lymphoid, and/or reticuloendothelial cell, comprising a gene operatively linked to an expression control sequence effective to express said gene in spleen, lymphoid, and/or reticuloendothelial, wherein said sequence is SEQ ID NO 205-213.

169. A method of selecting a gene predominantly expressed in spleen, lymphoid, and/or
10 reticuloendothelial cells from a database comprising polynucleotide sequences for genes, comprising:
displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205) of claim 170, or complements to the
15 polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

170. A composition consisting essentially of the 11q12.2 spleen gene complex, comprising
TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), and
20 TMD0621 (XM_166205).

171. A composition of claim 170, wherein said complex consists essentially of the chromosome region between STS markers G62658 and SHGC-154002.

25 172. A method of detecting a pancreas cell, comprising:
contacting a sample comprising cells with a polynucleotide specific TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199
30 under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization.

173. A method of claim 172, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

5 174. A method of detecting a pancreas cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or

10 TMD1127

of claim 199 under conditions effective for said binding partner bind specifically to said polypeptide, and

detecting specific binding.

15 175. A method of claim 174, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

176. A method of delivering an agent to a pancreas cell, comprising:

20 contacting a pancreas with an agent coupled to binding partner specific for TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199, whereby said agent is delivered to said cell.

25 177. A method of claim 176, wherein the agent is a therapeutic agent or an imaging agent.

178. A method of claim 176, wherein the agent is cytotoxic.

179. A method of claim 176, wherein the binding partner is an antibody.

30

180. A method of modulating a pancreas, immune, or reticuloendothelial cell, comprising:

contacting said cell with an agent effective to modulate TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, or the biological activity of a polypeptide encoded thereby, of claim 199, whereby the cell is modulated.

181. A method of assessing pancreas function, comprising:

detecting a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of pancreas function.

182. A method of claim 181, wherein said detecting is performed using an antibody which is specific for said polypeptide.

183. A method of claim 181, wherein said detecting is performed by RIA, ELISA, or Western blot.

184. A method of expressing a heterologous polynucleotide in pancreas cells, comprising:

expressing a nucleic acid construct in pancreas cell, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NO 258, 261, 262, 265-267, 270-272, 275, 278, 279, 282-284, 287, 290-293, 296, 297, 300, 303, 306, 309-314, 317-320, 323-326, 329, 332-333, 336-338, 341, and 344.

185. A method of assessing a therapeutic or preventative intervention in a subject having a pancreas or lymphoid disease, comprising,

determining the expression levels of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, or a polypeptide encoded thereby, of claim 199 in

a tissue sample comprising pancreas, lymphoid, or reticuloendothelial cells.

186. A method of claim 185, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

5

187. A method for identifying an agent that modulates the expression of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, comprising,

10

contacting a pancreas, lymphoid, or reticuloendothelial cell, with a test agent under conditions effective for said test agent to modulate the expression of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, of claim 199, and

15

determining whether said test agent modulates said gene.

188. A method of claim 187, wherein said agent is an antisense which is effective to inhibit translation of said gene.

20

189. A method for identifying an agent that modulates the expression of a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, comprising,

25

contacting a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199, with a test agent under conditions effective for said test agent to modulate said polypeptide, and

30

determining whether said test agent modulates said polypeptide.

190. A method of claim 189, wherein said test agent is an antibody.

191. A method of detecting polymorphisms in comprising, comparing the structure of :
genomic DNA or RNA or cDNA comprising all or part of an allele of

5 TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290,
TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675,
TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127,
with SEQ ID NOS of Table 23 of claim 199.

10 192. A method of claim 191, wherein said polymorphism is a nucleotide deletion,
substitution, inversion, or transposition.

193. A method of identifying a genetic basis for a pancreas disease or disease-susceptibility,
comprising: determining the association of a pancreas disease or disease-susceptibility with a
15 gene of claim 199.

194. A method of claim 193, wherein determining is performed by producing a human-
linkage map of said gene.

20 195. A method of claim 193, wherein determining is performed by comparing the
nucleotide sequences between normal subjects and subjects having a pancreas disease.

196. A non-human, transgenic mammal, or a cell thereof, whose genome comprises a
functional disruption of a gene represented by TMD0077, TMD0233, TMD0256, TMD0258,
25 TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639,
TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739,
TMD0753, TMD1111, and/or TMD1127, of claim 199, and which has a defect in pancreas,
lymphoid, and/or reticuloendothelial disease function.

30 197. A mammalian cell of claim 196, wherein said cell is a mouse cell.

198. A method of selecting a gene predominantly expressed in pancreas tissue from a

database comprising polynucleotide and amino acid sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, of claim 199, or complements to the polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

199. A composition comprising genes and/or polypeptide which are expressed

10 predominantly in pancreas tissue comprising:

TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127.

STS	RNA	Accn	locus	Gene code
55520K	RH79928 155920K			
55530K	SHGC-5451 155930K	XM_173381	LOC254079	
55540K	RH93848 155940K			
55550K	RH04445 155940K	XM_086610	CD1D	
55560K	SHGC-8275 155950K			
55570K	D1S3312 155950K			
55580K	RH66323 155960K			
55590K				
55600K				
55610K				
55620K				
55630K				
55640K				
55650K				
55660K				
55670K				
55680K				
55690K				
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55960K				
55970K				
55980K				
55990K				
56000K				
56010K				
56020K				
56030K				
56040K				
56050K				
56060K				
56070K				
56080K				
56090K				
56100K				
56110K				
56120K				
56130K				
56140K				
56150K				
56160K				
56170K				
56180K				
56190K				
56200K				
56210K				
56220K				
56230K				
56240K				
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56260K				
56270K				
56280K				
56290K				
56300K				
56310K				
56320K				
56330K				
56340K				
56350K				
56360K				
56370K				
56380K				
56390K				
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Fig. 1

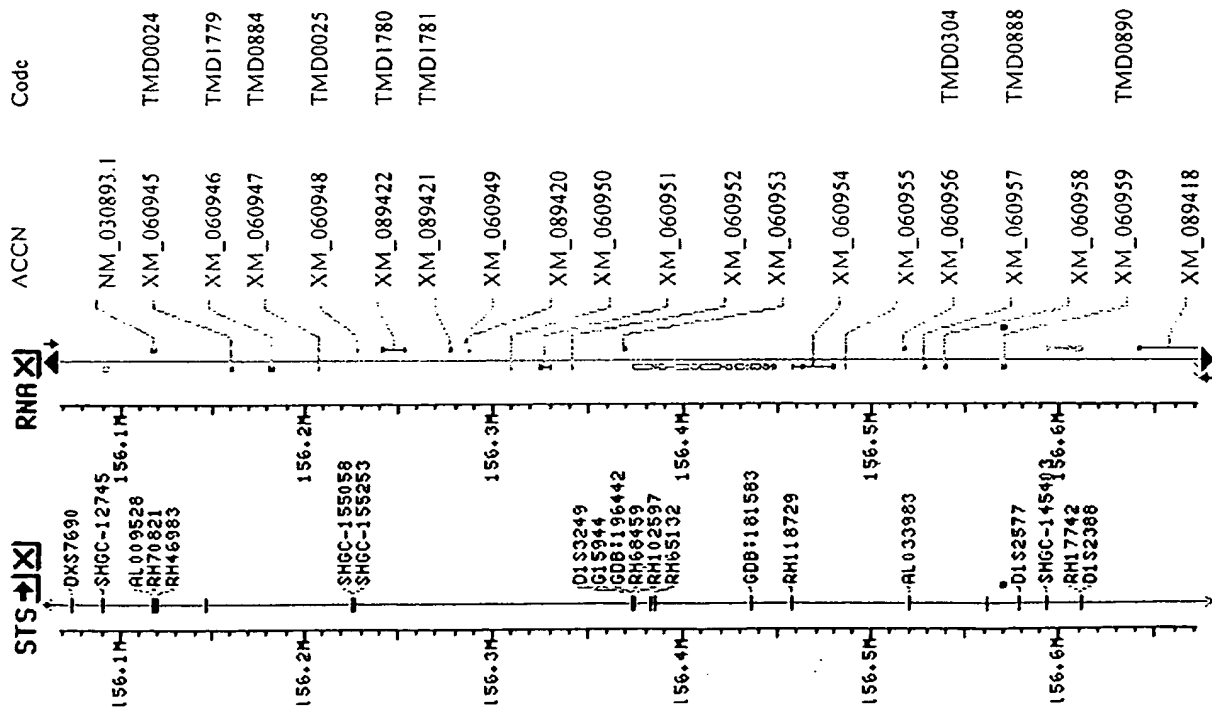


Fig. 2

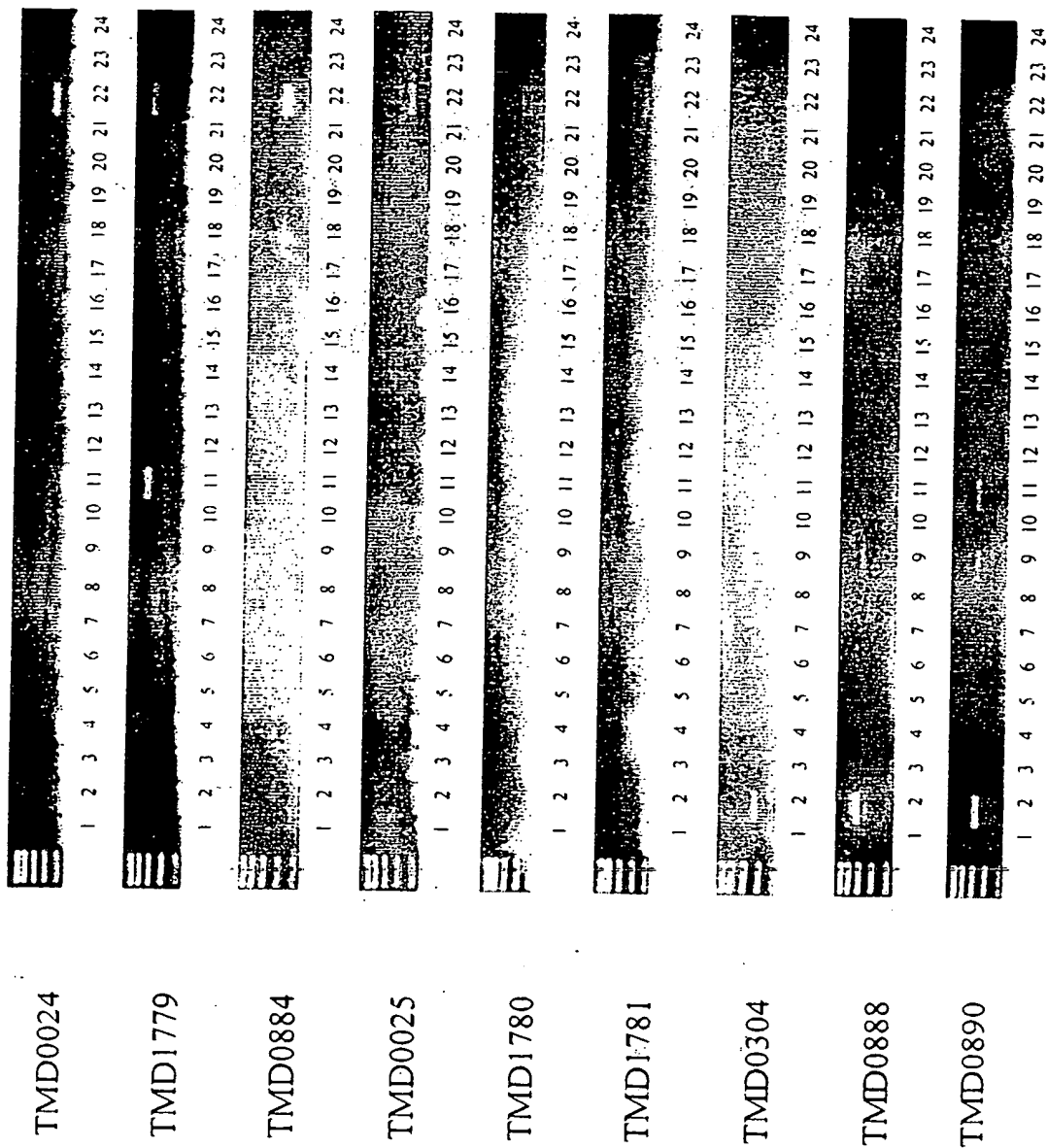


Fig. 3

XM_062147



XM_061676

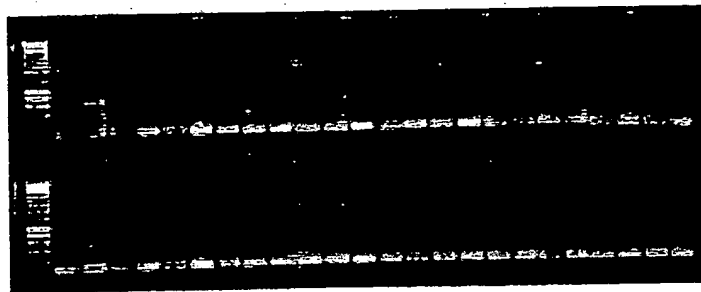


FIG. 4

Fig. 5a

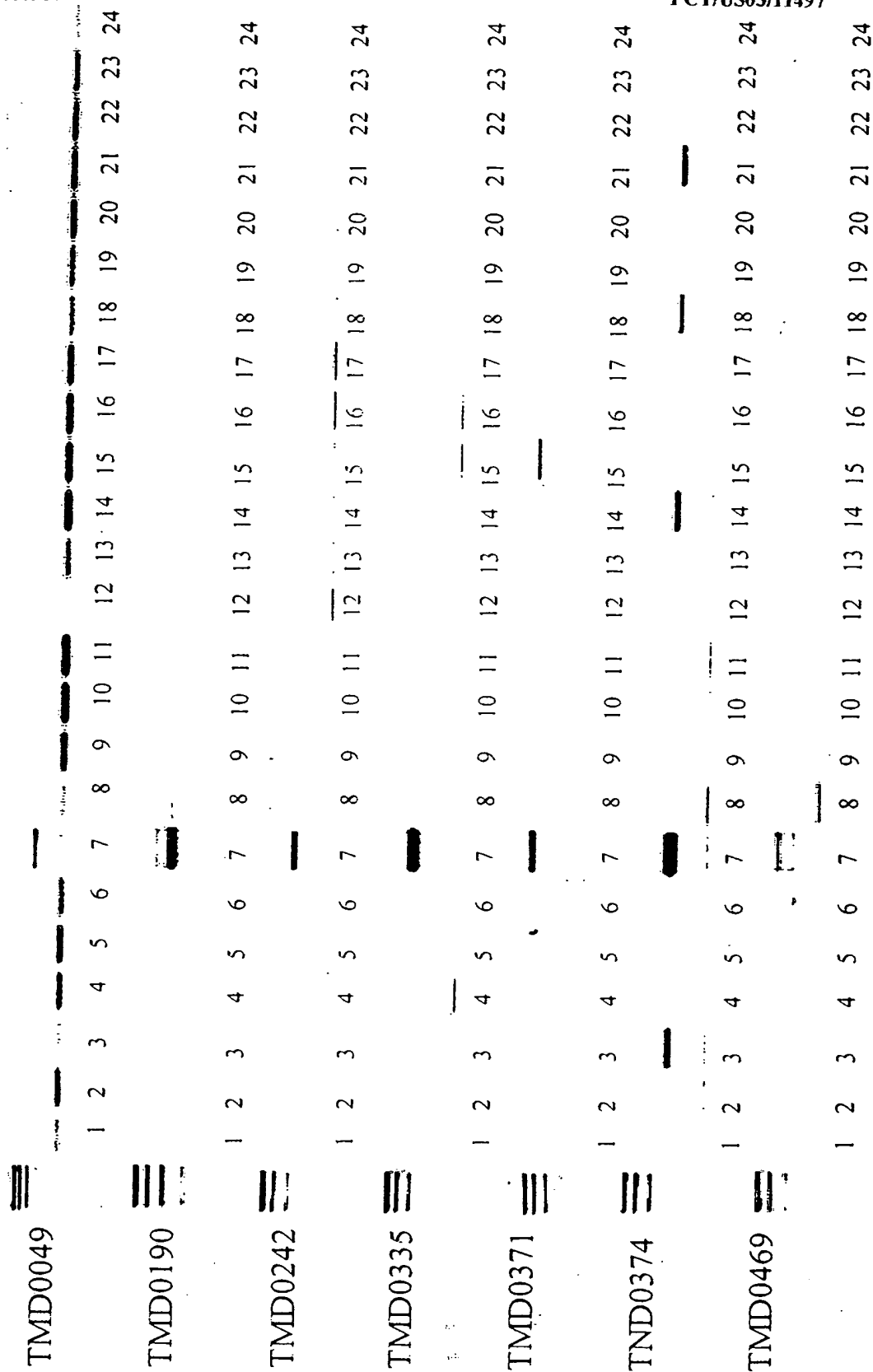
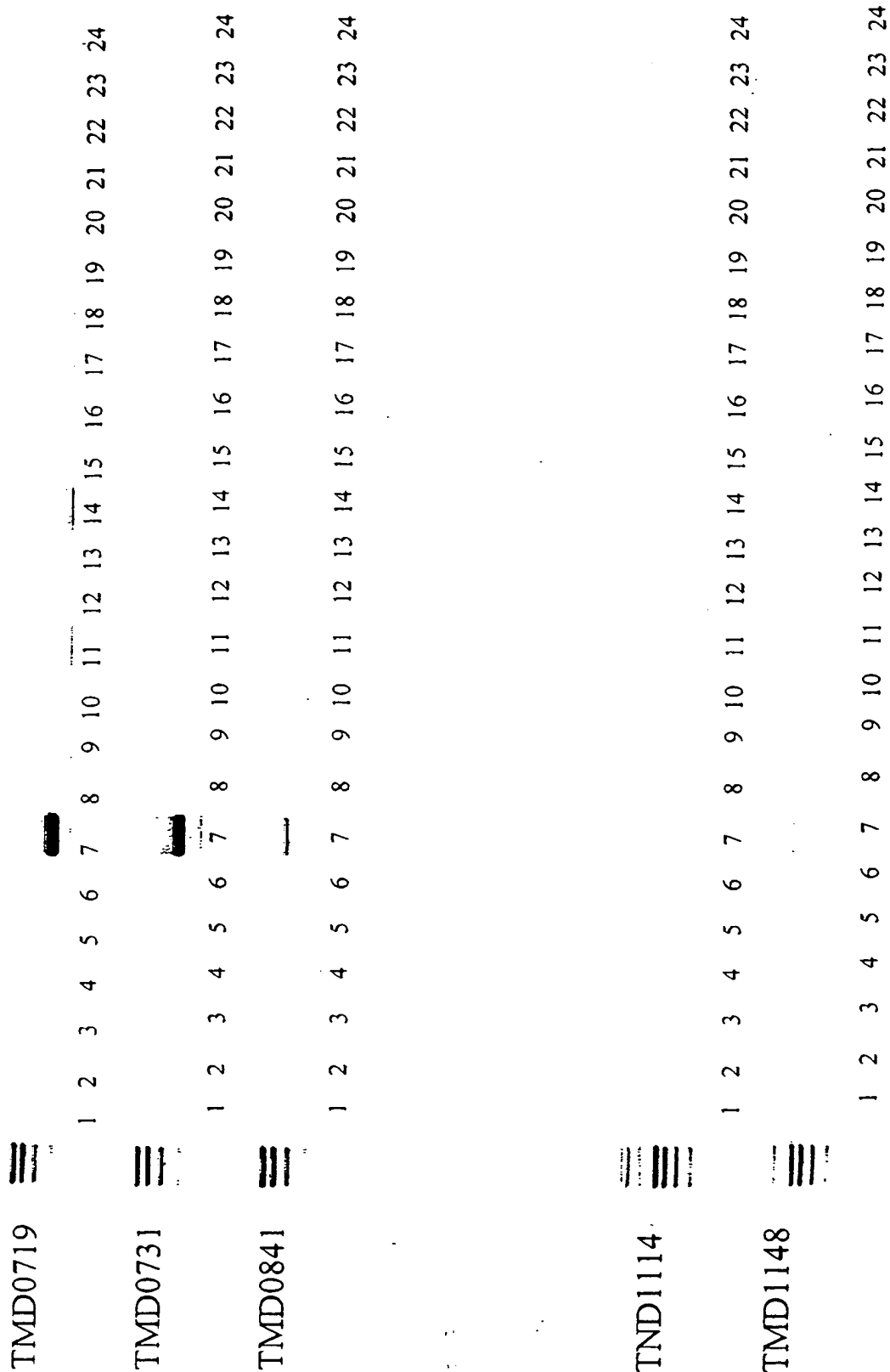


Fig. 5b



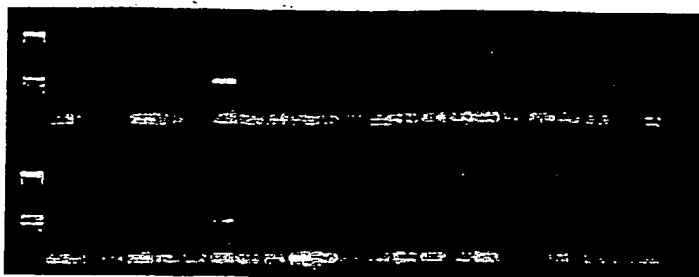


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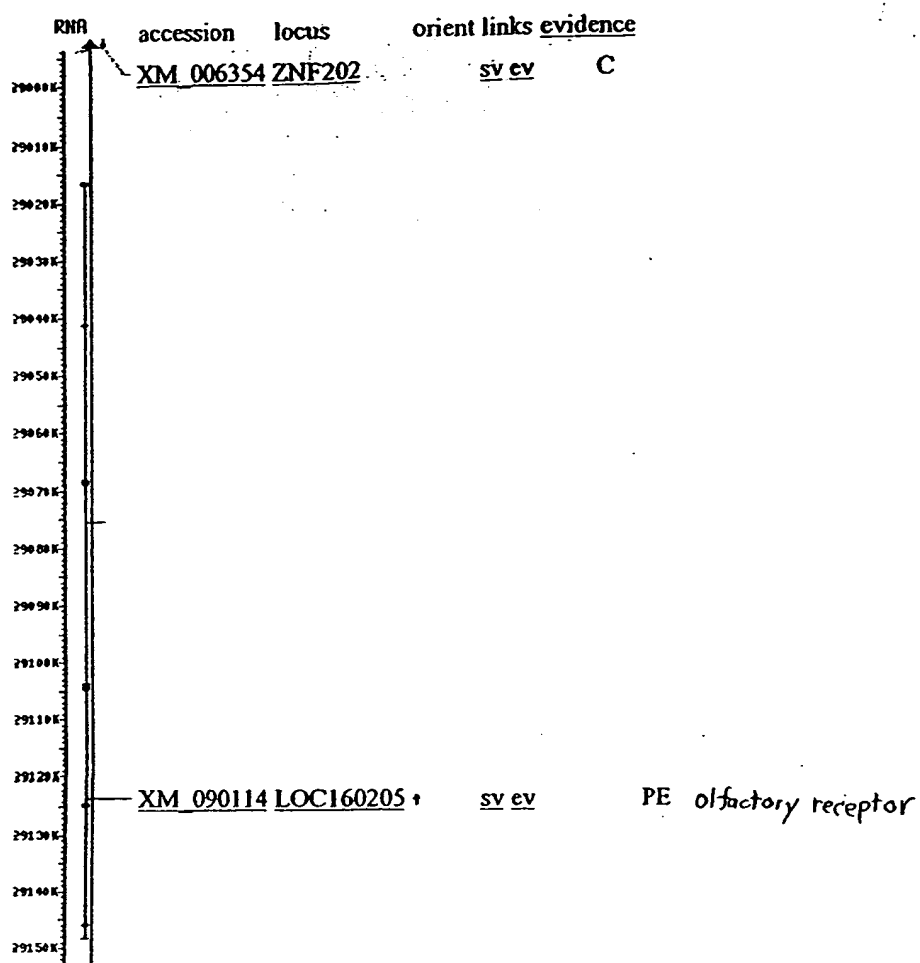


Fig 5A

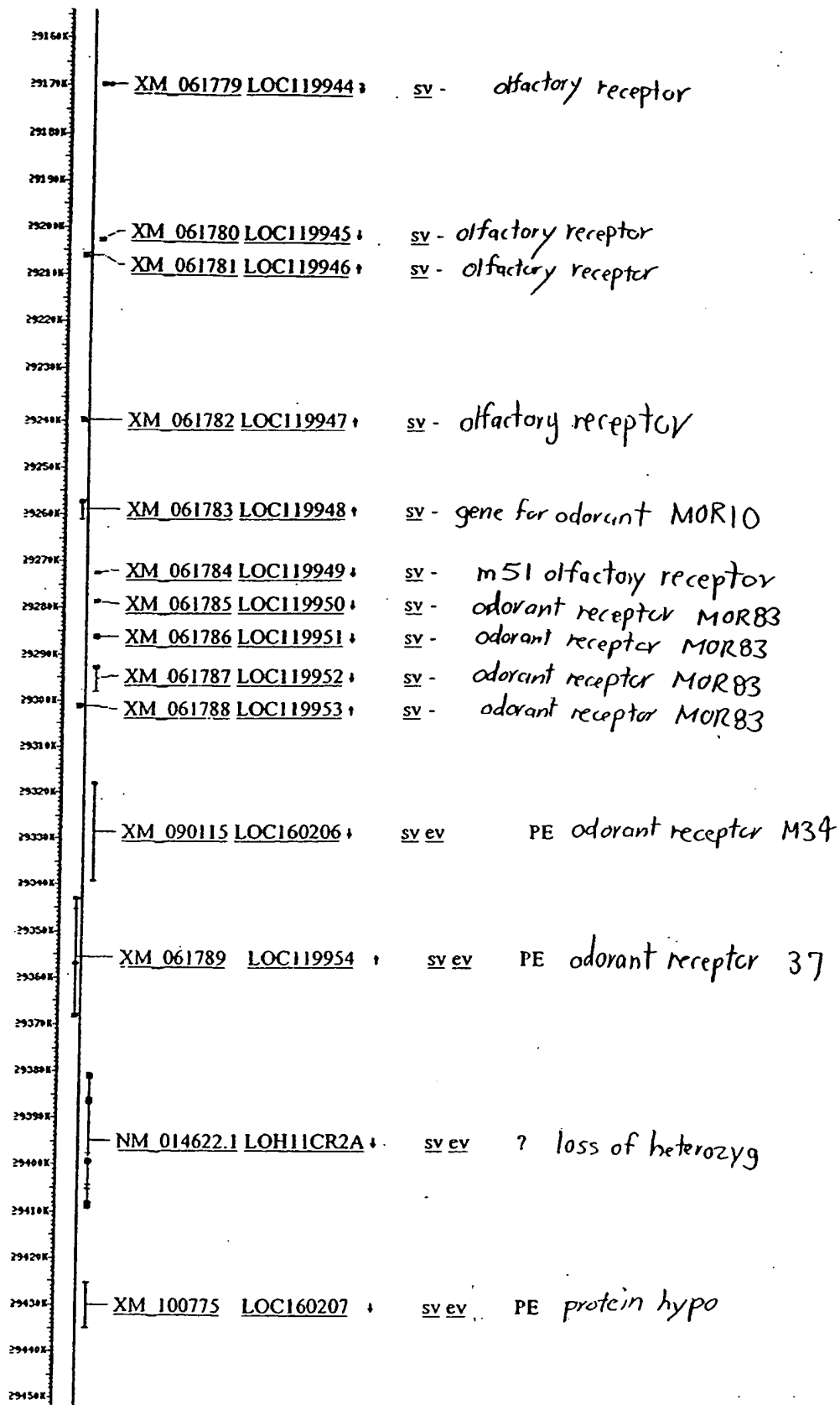


Fig 1B

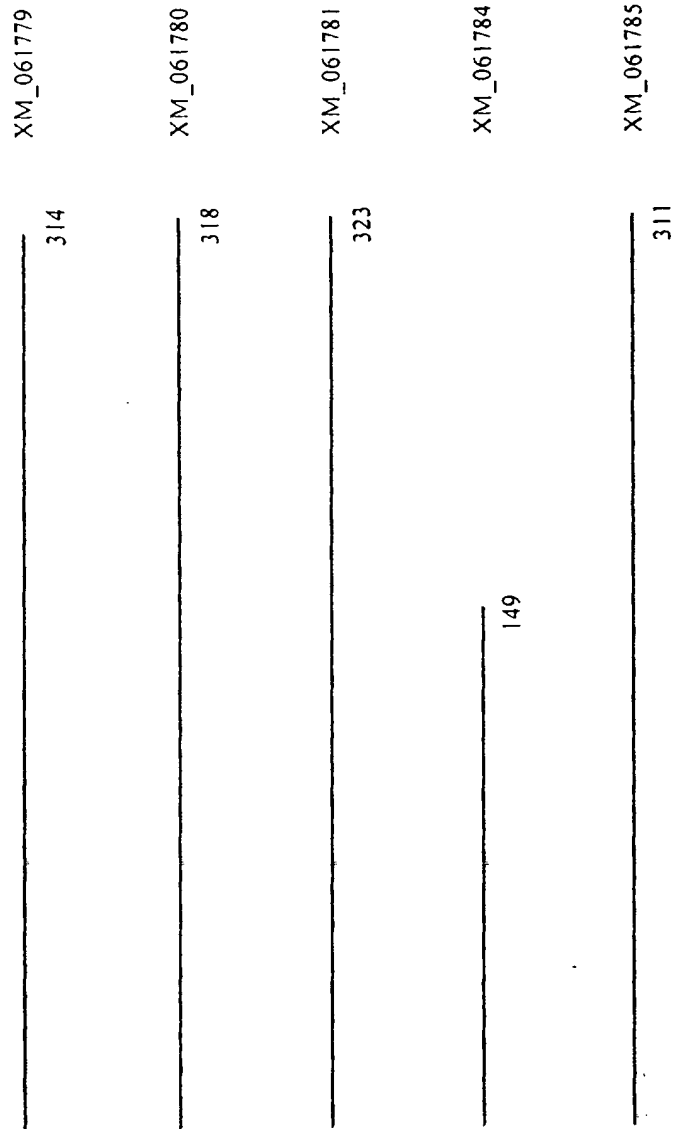
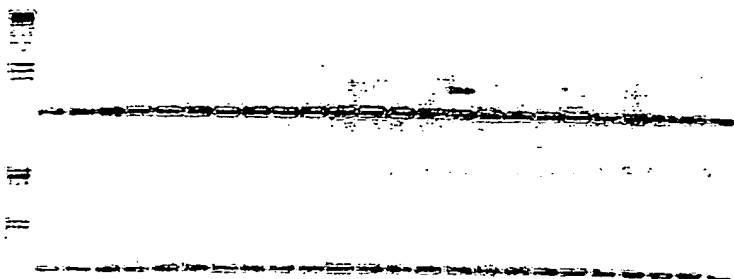
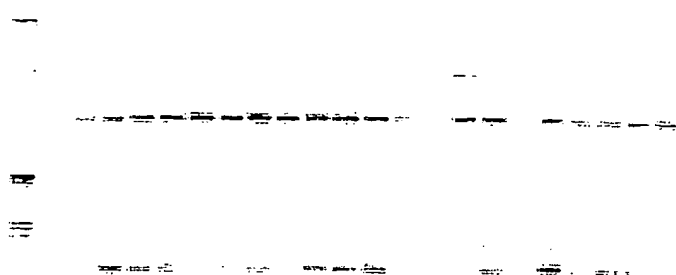


Fig. 8

XM_061779



XM_061780



XM_061781

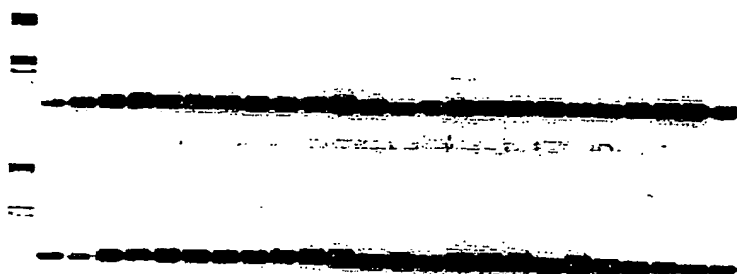


Fig. 9A

XM_061784



XM_061785



Fig. 9B

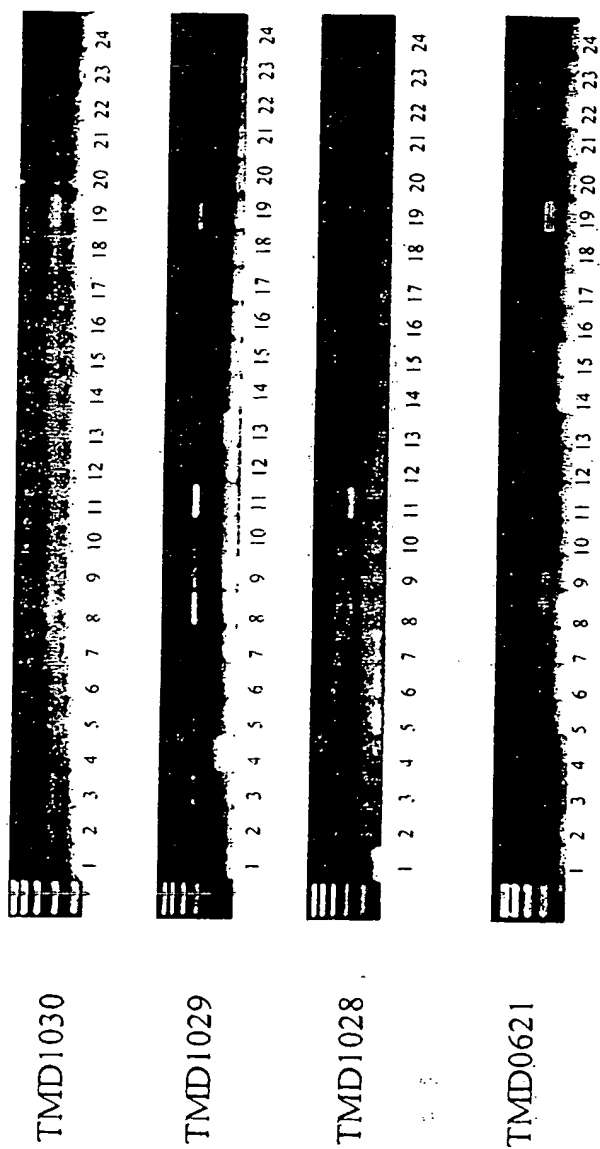


Fig.10

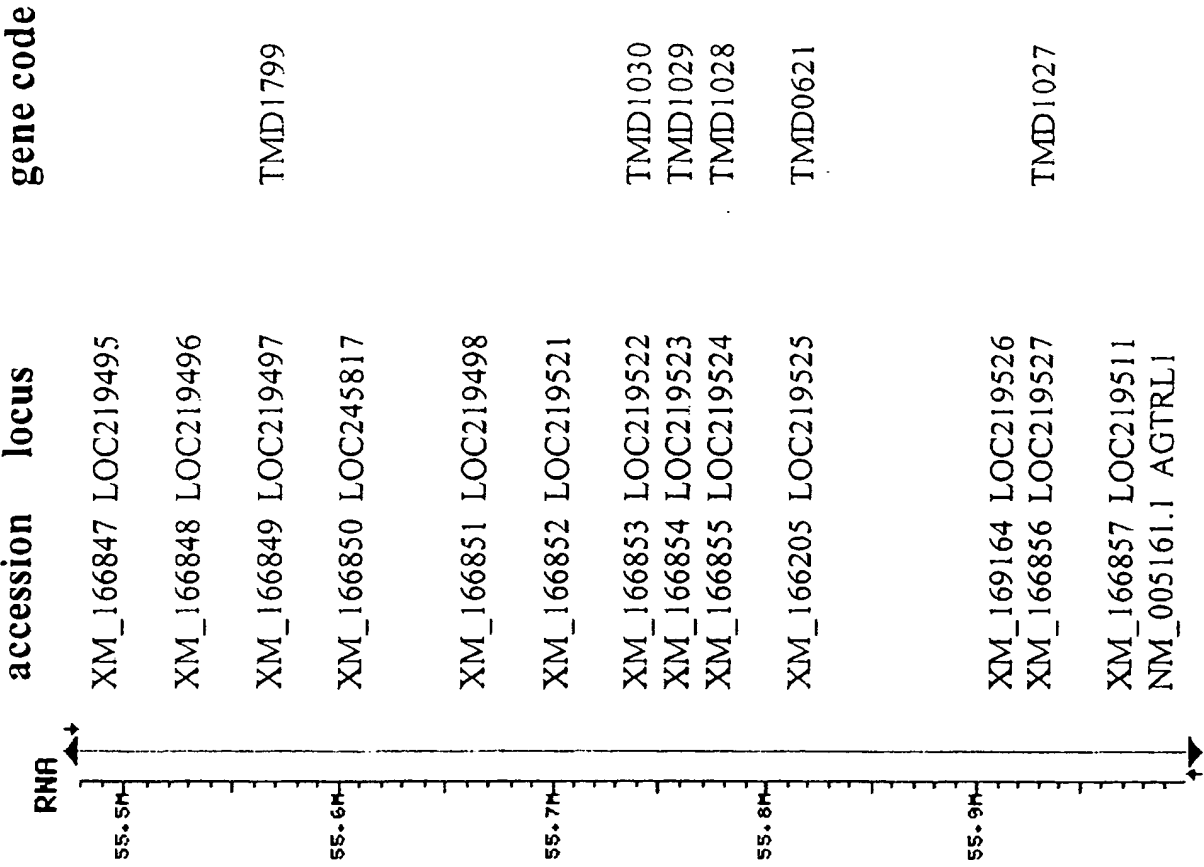


Fig. 11

FIG. 12A

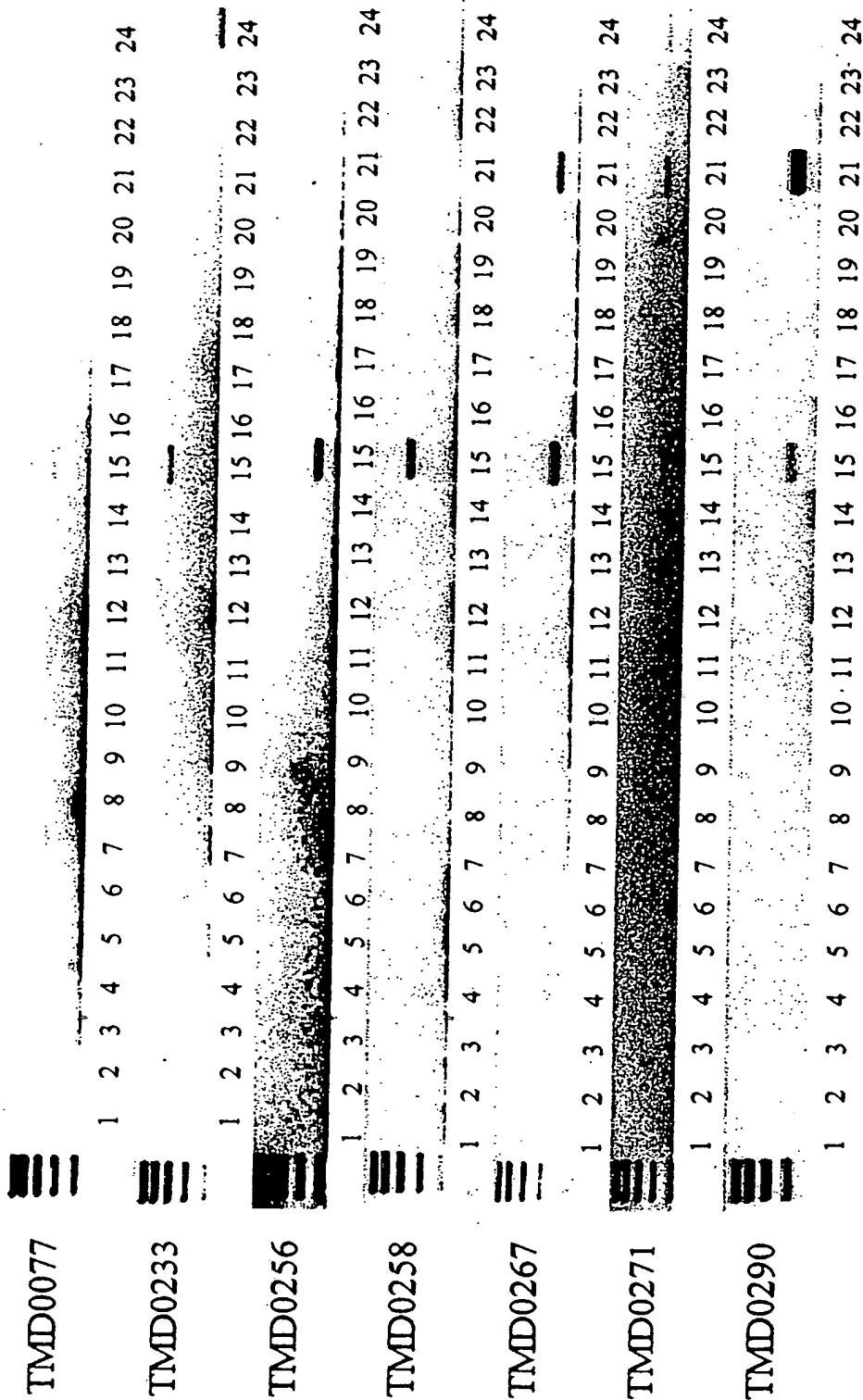


FIG. 12B

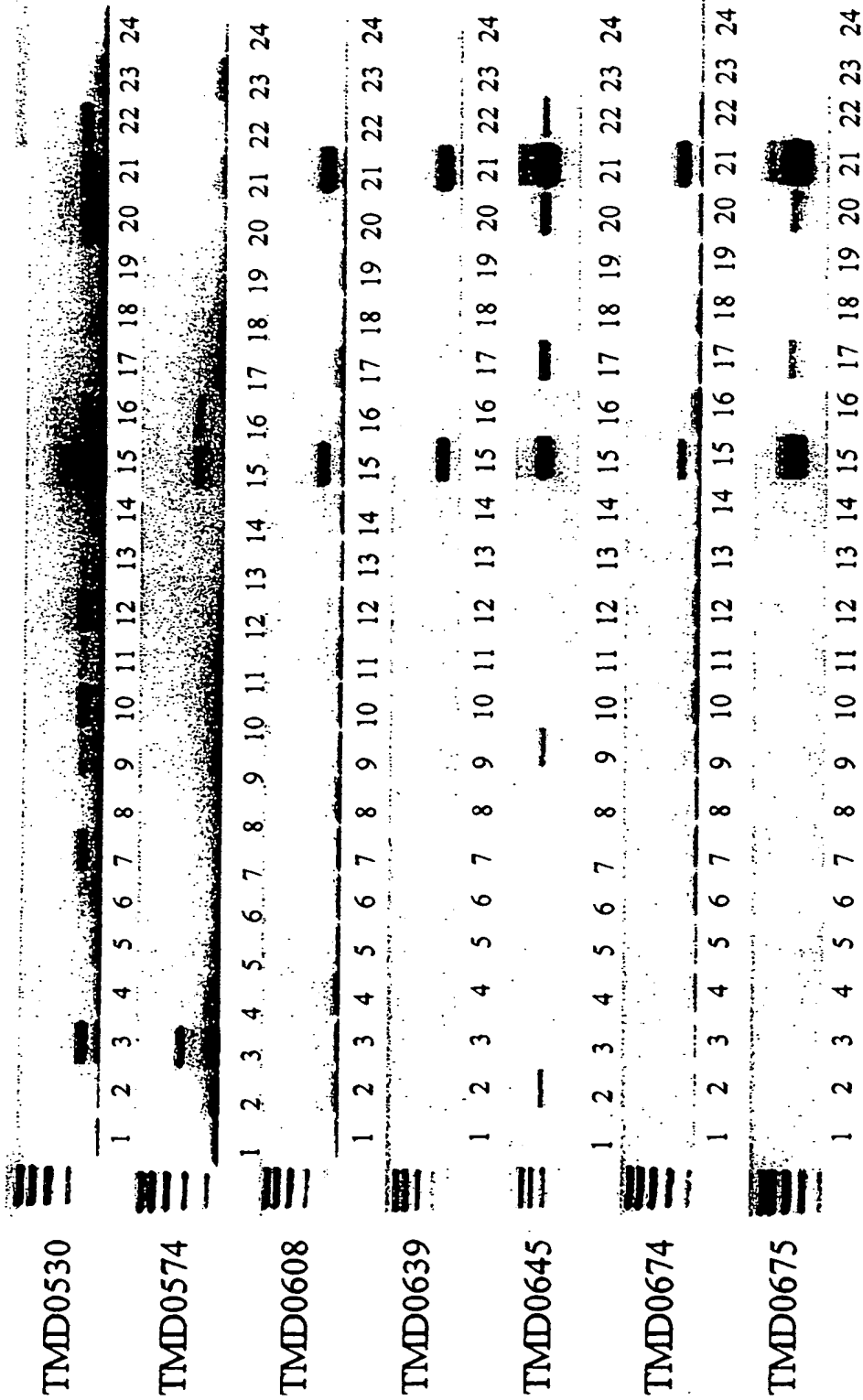
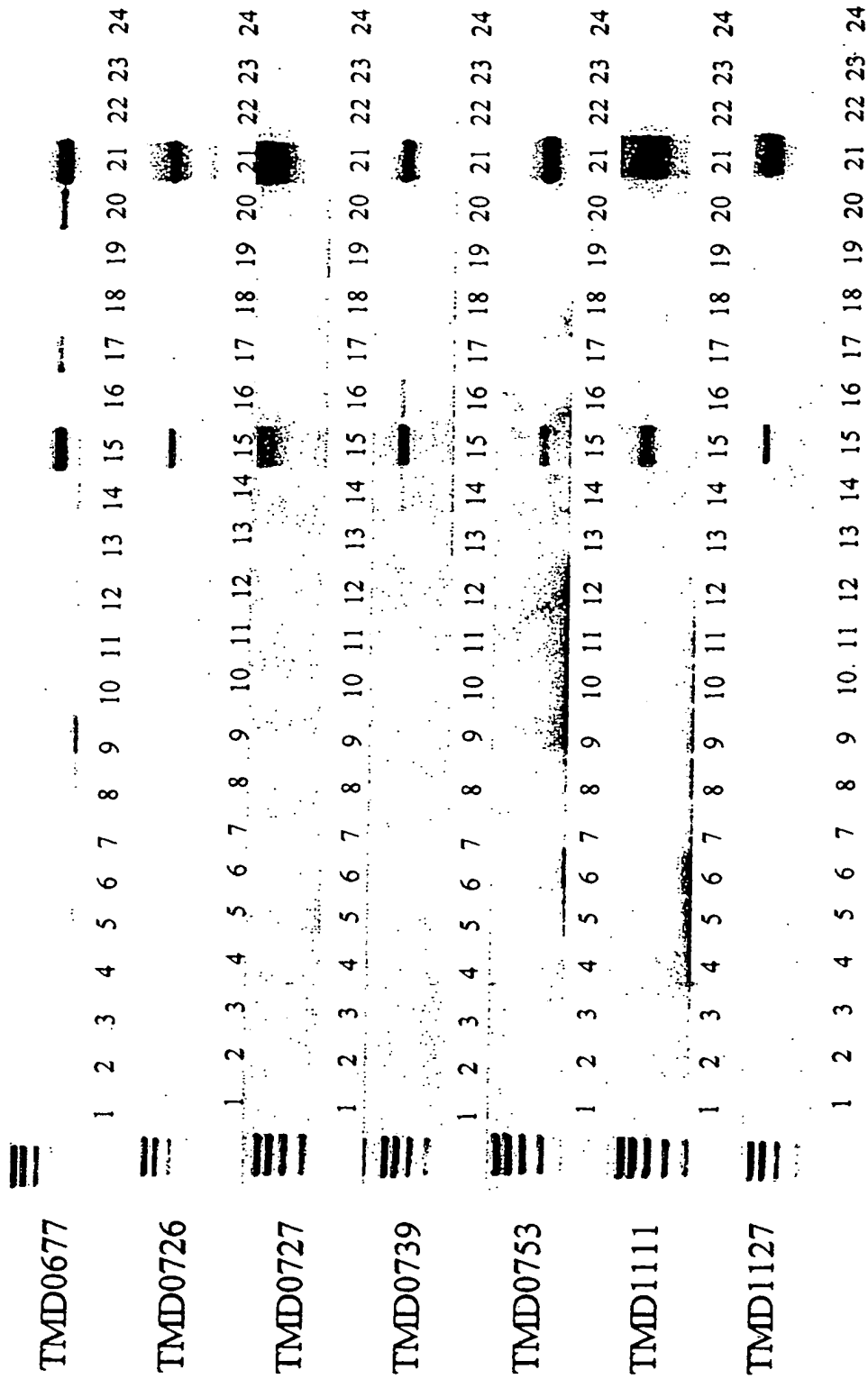


FIG. 12C



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gagatctggg gattcaatta atagctaata ttatgtatc tttatgtatc ctccatgaa			4082
tgaggatca aatattaact acaagaaatc ttgaattct atagaacttc ctaagaagat			4142
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tcaaatggga acttgaattg ttctatttat atatgtagca ttctatttat aaatatattt			4562
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160 200 PCT FINAL.ST25

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Leu Ile Tyr Leu Met Thr Val Leu Gly Asn Leu Leu Ile Phe Leu Val
 35 40 45

Val Cys Leu Asp Ser Arg Leu His Thr Pro Met Tyr His Phe Val Ser
 50 55 60

Ile Leu Ser Phe Ser Glu Leu Gly Tyr Thr Ala Ala Thr Ile Pro Lys
 65 70 75 80

Met Leu Ala Asn Leu Leu Ser Glu Lys Lys Thr Ile Ser Phe Ser Gly
 85 90 95

Cys Leu Leu Gln Ile Tyr Phe Phe His Ser Leu Gly Ala Thr Glu Cys
 100 105 110

Tyr Leu Leu Thr Ala Met Ala Tyr Asp Arg Tyr Leu Ala Ile Cys Arg
 115 120 125

Pro Leu His Tyr Pro Thr Leu Met Thr Pro Thr Leu Cys Ala Glu Ile
 130 135 140

Ala Ile Gly Cys Trp Leu Gly Gly Leu Ala Gly Pro Val Val Glu Ile
 145 150 155 160

Ser Leu Ile Ser Arg Leu Pro Phe Cys Gly Pro Asn Arg Ile Gln His
 165 170 175

Val Phe Cys Asp Phe Pro Pro Val Leu Ser Leu Ala Cys Thr Asp Thr
 180 185 190

Ser Ile Asn Val Leu Val Asp Phe Val Ile Asn Ser Cys Lys Ile Leu
 195 200 205

Ala Thr Phe Leu Leu Ile Leu Cys Ser Tyr Val Gln Ile Ile Cys Thr
 210 215 220

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Val Leu Arg Ile Pro Ser Ala Ala Gly Lys Arg Lys Ala Ile Ser Thr
 225 230 235 240

Cys Ala Ser His Phe Thr Val Val Leu Ile Phe Tyr Gly Ser Ile Leu
 245 250 255

Ser Met Tyr Val Gln Leu Lys Lys Ser Tyr Ser Leu Asp Tyr Asp Gln
 260 265 270

Ala Leu Ala Val Val Tyr Ser Val Leu Thr Pro Phe Leu Asn Pro Phe
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 Gly Phe Thr Thr Thr Gly Thr Leu Gln Pro Leu Ala Phe Leu Gly Thr
 20 25 30

cta tgc atc tat ctc ctc aca ctt gca ggg aac att ctc atc att gtc 146
 Leu Cys Ile Tyr Leu Leu Thr Leu Ala Gly Asn Ile Leu Ile Ile Val
 35 40 45

ctg agg tgt ggt atg tca gca cca cag tgc cca tgc tgc tgc aca cct 194
 Leu Arg Cys Gly Met Ser Ala Pro Gln Cys Pro Cys Cys Cys Thr Pro
 50 55 60

tgc tcc aag ggt gtt cac ccg tct cat cag ctg tat gct tta ttc agc 242
 Cys Ser Lys Gly Val His Pro Ser His Gln Leu Tyr Ala Leu Phe Ser
 65 70 75

tat gtc ttt cat tcc tta ggg atg act gag tgc tac ctg ctg ggt gtc 290
 Tyr Val Phe His Ser Leu Gly Met Thr Glu Cys Tyr Leu Leu Gly Val
 80 85 90 95

atg gca ctg gat agc tac ctt atc atc tgc cac cca ctc cac tac cac 338
 Met Ala Leu Asp Ser Tyr Leu Ile Ile Cys His Pro Leu His Tyr His
 100 105 110

gca ctc atg agc aga cag gta cag tta cga cta gct ggg gcc agt tgg 386
 Ala Leu Met Ser Arg Gln Val Gln Leu Arg Leu Ala Gly Ala Ser Trp
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 Val Ala Gly Phe Ser Ala Ala Leu Val Pro Ala Thr Leu Thr Ala Thr
 130 135 140

ctg ccc ttc tgc ttg aaa gag gtg gcc cat tac ttt tgt gac ttg gca 482
 Leu Pro Phe Cys Leu Lys Glu Val Ala His Tyr Phe Cys Asp Leu Ala
 145 150 155

cca cta atg cgg ttg gca tgt gtg gac aca agc tgg cat gct agg gcc 530
 Pro Leu Met Arg Leu Ala Cys Val Asp Thr Ser Trp His Ala Arg Ala
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cat ggc aca gtg att ggt gtg gcc act ggt tgc aac ttt gtg ctc att 578
 His Gly Thr Val Ile Gly Val Ala Thr Gly Cys Asn Phe Val Leu Ile
 180 185 190

ttg gga ctc tat gga ggt atc ctg aat gct gtg ctg aag cta ccc tca 626
 Leu Gly Leu Tyr Gly Gly Ile Leu Asn Ala Val Leu Lys Leu Pro Ser
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gtg gtg gca cta ttc tat gct tct gcc ttc aca gta tat gtg ggc tca 722
 Val Val Ala Leu Phe Tyr Ala Ser Ala Phe Thr Val Tyr Val Gly Ser
 225 230 235

cct ggg agt cga cct gag agc aca gac aag ctt gtt gcc ttg gtt tat 770
 Pro Gly Ser Arg Pro Glu Ser Thr Asp Lys Leu Val Ala Leu Val Tyr
 240 245 250 255

gcc ctt att acc cct ttc ctc aat cct atc atc tat agc ctt cgc aac 818
 Ala Leu Ile Thr Pro Phe Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn
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Cys Ile Tyr Leu Leu Thr Leu Ala Gly Asn Ile Leu Ile Ile Val Leu
 35 40 45

Arg Cys Gly Met Ser Ala Pro Gln Cys Pro Cys Cys Cys Thr Pro Cys
 50 55 60

Ser Lys Gly Val His Pro Ser His Gln Leu Tyr Ala Leu Phe Ser Tyr
 65 70 75 80

Val Phe His Ser Leu Gly Met Thr Glu Cys Tyr Leu Leu Gly Val Met
 85 90 95

Ala Leu Asp Ser Tyr Leu Ile Ile Cys His Pro Leu His Tyr His Ala
 100 105 110

Leu Met Ser Arg Gln Val Gln Leu Arg Leu Ala Gly Ala Ser Trp Val
 115 120 125

Ala Gly Phe Ser Ala Ala Leu Val Pro Ala Thr Leu Thr Ala Thr Leu
 130 135 140

Pro Phe Cys Leu Lys Glu Val Ala His Tyr Phe Cys Asp Leu Ala Pro
 145 150 155 160

Leu Met Arg Leu Ala Cys Val Asp Thr Ser Trp His Ala Arg Ala His
 165 170 175

Gly Thr Val Ile Gly Val Ala Thr Gly Cys Asn Phe Val Leu Ile Leu
 180 185 190

Gly Leu Tyr Gly Gly Ile Leu Asn Ala Val Leu Lys Leu Pro Ser Ala
 195 200 205

Ala Ser Ser Ala Lys Ala Phe Ser Thr Cys Ser Ser His Val Thr Val
 210 215 220

Val Ala Leu Phe Tyr Ala Ser Ala Phe Thr Val Tyr Val Gly Ser Pro
 225 230 235 240

Gly Ser Arg Pro Glu Ser Thr Asp Lys Leu Val Ala Leu Val Tyr Ala
 245 250 255

Leu Ile Thr Pro Phe Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn Lys
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Glu Leu Leu Tyr Cys Phe Leu Cys
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<212> DNA

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1			5					10					15			

cag	ctg	gcc	ctc	ttt	gta	gtt	ttt	ctt	ttt	ctg	tat	cta	gtc	att	ctt	96
Gln	Leu	Ala	Leu	Phe	Val	Val	Phe	Leu	Phe	Leu	Tyr	Leu	Val	Ile	Leu	
		20					25					30				

agt	ggc	aat	gtc	acc	att	atc	agt	gtc	atc	cac	ctg	gat	aaa	agc	ctc	144
Ser	Gly	Asn	Val	Thr	Ile	Ile	Ser	Val	Ile	His	Leu	Asp	Lys	Ser	Leu	
	35						40				45					

cac	aca	cca	atg	tac	ttc	ttc	ctt	ggc	att	ctc	tca	aca	tct	gag	acc	192
His	Thr	Pro	Met	Tyr	Phe	Phe	Leu	Gly	Ile	Leu	Ser	Thr	Ser	Glu	Thr	
	50					55				60						

ttc	tac	acc	ttt	gtc	att	cta	ccc	aag	atg	ctc	atc	aat	cta	ctt	tct	240
Phe	Tyr	Thr	Phe	Val	Ile	Leu	Pro	Lys	Met	Leu	Ile	Asn	Leu	Leu	Ser	
65			70					75				80				

gtg	gcc	agg	aca	atc	tcc	ttc	aac	tgt	tgt	gct	ctt	caa	atg	ttc	ttc	288
Val	Ala	Arg	Thr	Ile	Ser	Phe	Asn	Cys	Cys	Ala	Leu	Gln	Met	Phe	Phe	
			85					90					95			

ttc	ctt	ggc	ttt	gcc	att	acc	aac	tgc	ctg	cta	ttg	ggc	gtg	atg	ggc	336
Phe	Leu	Gly	Phe	Ala	Ile	Thr	Asn	Cys	Leu	Leu	Leu	Gly	Val	Met	Gly	

100 105 160 200 PCT FINAL.ST25
110

tat gat cgc tat gct gcc att tgt cac cct ctg cat tac ccc act ctt 384
Tyr Asp Arg Tyr Ala Ala Ile Cys His Pro Leu His Tyr Pro Thr Leu
115 120 125

atg agc tgg cag gtg tgt gga aaa ctg gca gct gcc tgt gca att ggt 432
Met Ser Trp Gln Val Cys Gly Lys Leu Ala Ala Cys Ala Ile Gly
130 135 140

ggc ttc ttg gcc tct ctt aca gta gta aat tta gtt ttc agc ctc cct 480
Gly Phe Leu Ala Ser Leu Thr Val Val Asn Leu Val Phe Ser Leu Pro
145 150 155 160

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Phe Cys Ser Ala Asn Lys Val Asn His Tyr Phe Cys Asp Ile Ser Ala
165 170 175

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Val Ile Leu Leu Ala Cys Thr Asn Thr Asp Val Asn Glu Phe Val Ile
180 185 190

ttc att tgt gga gtt ctt gta ctt gtg gtt ccc ttt ctg ttt atc tgt 624
Phe Ile Cys Gly Val Leu Val Leu Val Val Pro Phe Leu Phe Ile Cys
195 200 205

gtt tct tat ctc tgc att ctg agg act atc ctg aag att ccc tca gct 672
Val Ser Tyr Leu Cys Ile Leu Arg Thr Ile Leu Lys Ile Pro Ser Ala
210 215 220

gag ggc aga cgg aaa gcg ttt tcc acc tgc gcc tct cac ctc agt gtt 720
Glu Gly Arg Arg Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser Val
225 230 235 240

gtt att gtt cat tat ggc tgt gct tcc ttc atc tac ctg agg cct aca 768
Val Ile Val His Tyr Gly Cys Ala Ser Phe Ile Tyr Leu Arg Pro Thr
245 250 255

gca aac tat gtg tcc aac aaa gac agg ctg gtg acg gtg aca tac acg 816
Ala Asn Tyr Val Ser Asn Lys Asp Arg Leu Val Thr Val Thr Tyr Thr
260 265 270

att gtc act cca tta cta aac ccc atg gtt tat agc ctc aga aac aag 864
Ile Val Thr Pro Leu Leu Asn Pro Met Val Tyr Ser Leu Arg Asn Lys
275 280 285

gat gtc caa ctt gct atc aga aaa gtg ttg ggc aag aaa ggt att ctt 912
Asp Val Gln Leu Ala Ile Arg Lys Val Leu Gly Lys Lys Gly Ile Leu
290 295 300

tct atc tct gaa atc ttc tac aca act gtt att ctg ccc aag atg ctt 960
Ser Ile Ser Glu Ile Phe Tyr Thr Thr Val Ile Leu Pro Lys Met Leu
305 310 315 320

atc aac tta ttc tct gta ttc agg aca ctc tcc ttt gtg agt tgt gcc 1008
Ile Asn Leu Phe Ser Val Phe Arg Thr Leu Ser Phe Val Ser Cys Ala
325 330 335

acc caa atg ttc ttc ttc ctc ggt ttt gct gtc act aac tgt ctg ctt 1056
Thr Gln Met Phe Phe Phe Leu Gly Phe Ala Val Thr Asn Cys Leu Leu
340 345 350

ctg gga gtg atg ggt tat gat cgt tat gct gcc atc tgt cag cct ttg 1104
Leu Gly Val Met Gly Tyr Asp Arg Tyr Ala Ala Ile Cys Gln Pro Leu
355 360 365

caa tac gct gtt ctc atg agc tgg aga gta tgt gga caa ctg ata gca 1152
Gln Tyr Ala Val Leu Met Ser Trp Arg Val Cys Gly Gln Leu Ile Ala
370 375 380

act tgt att att agt ggc ttc cta ata tct ctg gtg gga aca act ttt 1200
Thr Cys Ile Ile Ser Gly Phe Leu Ile Ser Leu Val Gly Thr Thr Phe
385 390 395 400

gtc ttt agc ctc cct ttc tgt ggc tcc aac aag gtc aac cac tac ttt 1248
Val Phe Ser Leu Pro Phe Cys Gly Ser Asn Lys Val Asn His Tyr Phe
405 410 415

tgt gat att tca cca gtt atc cgt ctc gcc tgt gct gac agc tac atc 1296

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Cys Asp Ile Ser Pro Val Ile Arg Leu Ala Cys Ala Asp Ser Tyr Ile
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agt gaa ctg gtc atc ttc atc ttc ggg gtc ttg gtg ctt gtt gtg ccc 1344
 Ser Glu Leu Val Ile Phe Ile Phe Gly Val Leu Val Leu Val Val Pro
 435 440 445

ttg ata ttt atc tgc att tcc tat ggc ttc att gtc cgc acc atc ctg 1392
 Leu Ile Phe Ile Cys Ile Ser Tyr Gly Phe Ile Val Arg Thr Ile Leu
 450 455 460

aag atc cca tca gct gaa ggc aaa caa aaa gcc ttc tcc acc tgt gct 1440
 Lys Ile Pro Ser Ala Glu Gly Lys Gln Lys Ala Phe Ser Thr Cys Ala
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tcc cat ctc att gta gtc att gtc cat tat ggt tga 1476
 Ser His Leu Ile Val Val Ile Val His Tyr Gly
 485 490

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 20 25 30

Ser Gly Asn Val Thr Ile Ile Ser Val Ile His Leu Asp Lys Ser Leu
 35 40 45

His Thr Pro Met Tyr Phe Phe Leu Gly Ile Leu Ser Thr Ser Glu Thr
 50 55 60

Phe Tyr Thr Phe Val Ile Leu Pro Lys Met Leu Ile Asn Leu Leu Ser
 65 70 75 80

Val Ala Arg Thr Ile Ser Phe Asn Cys Cys Ala Leu Gln Met Phe Phe
 85 90 95

Phe Leu Gly Phe Ala Ile Thr Asn Cys Leu Leu Leu Gly Val Met Gly
 100 105 110

Tyr Asp Arg Tyr Ala Ala Ile Cys His Pro Leu His Tyr Pro Thr Leu
 115 120 125

Met Ser Trp Gln Val Cys Gly Lys Leu Ala Ala Ala Cys Ala Ile Gly
 130 135 140

Gly Phe Leu Ala Ser Leu Thr Val Val Asn Leu Val Phe Ser Leu Pro
 145 150 155 160

Phe Cys Ser Ala Asn Lys Val Asn His Tyr Phe Cys Asp Ile Ser Ala
 165 170 175

Val Ile Leu Leu Ala Cys Thr Asn Thr Asp Val Asn Glu Phe Val Ile
 180 185 190

Phe Ile Cys Gly Val Leu Val Leu Val Val Pro Phe Leu Phe Ile Cys
 195 200 205

16U 200 PCT FINAL.ST25
 Val Ser Tyr Leu Cys Ile Leu Arg Thr Ile Leu Lys Ile Pro Ser Ala
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 Glu Gly Arg Arg.Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser Val
 225 230 235 240
 Val Ile Val His Tyr Gly Cys Ala Ser Phe Ile Tyr Leu Arg Pro Thr
 245 250 255
 Ala Asn Tyr Val Ser Asn Lys Asp Arg Leu Val Thr Val Thr Tyr Thr
 260 265 270
 Ile Val Thr Pro Leu Leu Asn Pro Met Val Tyr Ser Leu Arg Asn Lys
 275 280 285
 Asp Val Gln Leu Ala Ile Arg Lys Val Leu Gly Lys Lys Gly Ile Leu
 290 295 300
 Ser Ile Ser Glu Ile Phe Tyr Thr Thr Val Ile Leu Pro Lys Met Leu
 305 310 315 320
 Ile Asn Leu Phe Ser Val Phe Arg Thr Leu Ser Phe Val Ser Cys Ala
 325 330 335
 Thr Gln Met Phe Phe Phe Leu Gly Phe Ala Val Thr Asn Cys Leu Leu
 340 345 350
 Leu Gly Val Met Gly Tyr Asp Arg Tyr Ala Ala Ile Cys Gln Pro Leu
 355 360 365
 Gln Tyr Ala Val Leu Met Ser Trp Arg Val Cys Gly Gln Leu Ile Ala
 370 375 380
 Thr Cys Ile Ile Ser Gly Phe Leu Ile Ser Leu Val Gly Thr Thr Phe
 385 390 395 400
 Val Phe Ser Leu Pro Phe Cys Gly Ser Asn Lys Val Asn His Tyr Phe
 405 410 415
 Cys Asp Ile Ser Pro Val Ile Arg Leu Ala Cys Ala Asp Ser Tyr Ile
 420 425 430
 Ser Glu Leu Val Ile Phe Ile Phe Gly Val Leu Val Leu Val Val Pro
 435 440 445
 Leu Ile Phe Ile Cys Ile Ser Tyr Gly Phe Ile Val Arg Thr Ile Leu
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 465 470 475 480
 Ser His Leu Ile Val Val Ile Val His Tyr Gly
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160 200 PCT FINAL.ST25

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 Pro Val Leu Thr Ser Trp Gln Ile Cys Ser Phe Leu Asp Phe Gln Leu
 20 25 30

 ctt ttc tgt ggc cca aac aag atc aac cac tac ttc tgt gac atc tca 144
 Leu Phe Cys Gly Pro Asn Lys Ile Asn His Tyr Phe Cys Asp Ile Ser
 35 40 45

 ctg ctt att cag ctt gcc tgt act gat acc tac atc agg gag cta gtc 192
 Leu Leu Ile Gln Leu Ala Cys Thr Asp Thr Tyr Ile Arg Glu Leu Val
 50 55 60

 atc ttc att ggt gga att cta gca ctt acg gtt cct ctg att tta ttt 240
 Ile Phe Ile Gly Gly Ile Leu Ala Leu Thr Val Pro Leu Ile Leu Phe
 65 70 75 80

 gca tct cct atg gct tca ttg ttc aca cca tcc tga 276

160 200 PCT FINAL.ST25

Ala Ser Pro Met Ala Ser Leu Phe Thr Pro Ser
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20 25 30

Leu Phe Cys Gly Pro Asn Lys Ile Asn His Tyr Phe Cys Asp Ile Ser
35 40 45

Leu Leu Ile Gln Leu Ala Cys Thr Asp Thr Tyr Ile Arg Glu Leu Val
50 55 60

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65 70 75 80

Ala Ser Pro Met Ala Ser Leu Phe Thr Pro Ser
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16U 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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160 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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Phe Cys Leu Ala Tyr Thr Leu Ala Leu Leu Gly Asn Cys Thr Leu Leu
 35 40 45

Leu Ile Ile Gln Ala Asp Ala Leu His Glu Pro Met Tyr Leu Phe
 50 55 60

Leu Ala Met Leu Ala Ala Ile Asp Leu Val Leu Ser Ser Ser Ala Leu
 65 70 75 80

Pro Lys Met Leu Ala Ile Phe Trp Phe Arg Asp Arg Glu Ile Asn Phe
 85 90 95

Phe Ala Cys Leu Ala Gln Met Phe Phe Leu His Ser Phe Ser Ile Met
 100 105 110

Glu Ser Ala Val Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile
 115 120 125

Cys Lys Pro Leu His Tyr Thr Lys Val Leu Thr Gly Ser Leu Ile Thr
 130 135 140

Lys Ile Gly Met Ala Ala Val Ala Arg Ala Val Thr Leu Met Thr Pro
 145 150 155 160

16U 200 PCT FINAL.ST25
 Leu Pro Phe Leu Leu Arg Cys Phe His Tyr Cys Arg Gly Pro Val Ile
 165 170 175
 Ala His Cys Tyr Cys Glu His Met Ala Val Val Arg Leu Ala Cys Gly
 180 185 190
 Asp Thr Ser Phe Asn Asn Ile Tyr Gly Ile Ala Val Ala Met Phe Ile
 195 200 205
 Val Val Leu Asp Leu Leu Leu Val Ile Leu Ser Tyr Ile Phe Ile Leu
 210 215 220
 Gln Ala Val Leu Leu Leu Ala Ser Gln Glu Ala His Tyr Lys Ala Phe
 225 230 235 240
 Gly Thr Cys Val Ser His Ile Gly Ala Ile Leu Ala Phe Tyr Thr Thr
 245 250 255
 Val Val Ile Ser Ser Val Met His Arg Val Ala Arg His Ala Ala Pro
 260 265 270
 His Val His Ile Leu Leu Ala Asn Phe Tyr Leu Leu Phe Pro Pro Met
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 cccagtcctat ctacctggc gggattctg tgggagctgc tgcgtgcggc cctgcctcag 720
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 15 20 25 30

gcc tac ggt gtg cgg gac tgg aca ctg ctg cag ctg gtg gtc tcg gtc 864
 Ala Tyr Gly Val Arg Asp Trp Thr Leu Leu Gln Leu Val Val Ser Val
 35 40 45

ccc ttc ttc ctg tgc ttt ttg tac tcc tgg tgg ctg gca gag tcg gca 912
 Pro Phe Phe Leu Cys Phe Leu Tyr Ser Trp Trp Leu Ala Glu Ser Ala
 50 55 60

cga tgg ctg ctg acc aca ggc agg ctg gat tgg ggc ctg cag gag ctg 960
 Arg Trp Leu Leu Thr Thr Gly Arg Leu Asp Trp Gly Leu Gln Glu Leu
 65 70 75

16U 200 PCT FINAL.ST25

tgg agg gtg gct gcc atc aac gga aag ggg gca gtg cag gac acc ctg 1008
 Trp Arg Val Ala Ala Ile Asn Gly Lys Gly Ala Val Gln Asp Thr Leu
 80 85 90

acc cct gag gtc ttg ctt tca gcc atg cgg gag gag ctg agc atg ggc 1056
 Thr Pro Glu Val Leu Leu Ser Ala Met Arg Glu Glu Leu Ser Met Gly
 95 100 105 110

cag cct cct gcc agc ctg ggc acc ctg ctc cgc atg ccc gga ctg cgc 1104
 Gln Pro Pro Ala Ser Leu Gly Thr Leu Arg Met Pro Gly Leu Arg
 115 120 125

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 Phe Arg Thr Cys Ile Ser Thr Leu Cys Trp Phe Ala Phe Gly Phe Thr
 130 135 140

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 Phe Phe Gly Leu Ala Leu Asp Leu Gln Ala Leu Gly Ser Asn Ile Phe
 145 150 155

ctg ctc caa atg ttc att ggt gtc gtg gac atc cca gcc aag atg ggc 1248
 Leu Leu Gln Met Phe Ile Gly Val Val Asp Ile Pro Ala Lys Met Gly
 160 165 170

gcc ctg ctg ctg ctg agc cac ctg ggc cgc cgc ccc acg ctg gcc gca 1296
 Ala Leu Leu Leu Leu Ser His Leu Gly Arg Arg Pro Thr Leu Ala Ala
 175 180 185 190

tcc ctg ttg ctg gca ggg ctc tgc att ctg gcc aac acg ctg gtg ccc 1344
 Ser Leu Leu Leu Ala Gly Leu Cys Ile Leu Ala Asn Thr Leu Val Pro
 195 200 205

cac gaa atg ggg gct ctg cgc tca gcc ttg gcc gtg ctg ggg ctg ggc 1392
 His Glu Met Gly Ala Leu Arg Ser Ala Leu Ala Val Leu Gly Leu Gly
 210 215 220

ggg gtg ggg gct gcc ttc acc tgc atc acc atc tac agc agc gag ctc 1440
 Gly Val Gly Ala Ala Phe Thr Cys Ile Thr Ile Tyr Ser Ser Glu Leu
 225 230 235

ttc ccc act gtg ctc agg atg acg gca gtg ggc ttg ggc cag atg gca 1488
 Phe Pro Thr Val Leu Arg Met Thr Ala Val Gly Leu Gly Gln Met Ala
 240 245 250

gcc cgt gga gga gcc atc ctg ggg cct ctg gtc cgg ctg ctg ggt gtc 1536
 Ala Arg Gly Gly Ala Ile Leu Gly Pro Leu Val Arg Leu Leu Gly Val
 255 260 265 270

cat ggc ccc tgg ctg ccc ttg ctg gtg tat ggg acg gtg cca gtg ctg 1584
 His Gly Pro Trp Leu Pro Leu Leu Val Tyr Gly Thr Val Pro Val Leu
 275 280 285

agt ggc ctg gcc gca ctg ctt ctg ccc gag acc cag agc ttg ccg ctg 1632
 Ser Gly Leu Ala Ala Leu Leu Leu Pro Glu Thr Gln Ser Leu Pro Leu
 290 295 300

ccc gac acc atc caa gat gtg cag aac cag gca gta aag aag gca aca 1680
 Pro Asp Thr Ile Gln Asp Val Gln Asn Gln Ala Val Lys Lys Ala Thr
 305 310 315

_cat ggc acg ctg ggg aac tct gtc cta aaa tcc aca cag ttt 1722
 His Gly Thr Leu Gly Asn Ser Val Leu Lys Ser Thr Gln Phe
 320 325 330

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agaaggcagg aggaaagcaa agacctccat ttccagaggc ccagaggctg ccctctgagg 1842

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ggcccccttc aatactgaag gggaaaagga cagtttgatt ggcaggagggt gaccagtg 1962

accatcaccc tgccctgcc tcgtggcttc ggagagcaga ggggtcaggc ccaggggaac 2022

gagctggcct tgccaacct ctgcttgact ccgactgcc acttgctccc ccacaccgt 2082

ccacctgcc agagctcaga gctaaccacc atccatggc aagacctctc ctgctccac 2142

acaagcagta gagtctcagc tccacagctt taccagaag ccctgtaagc ctggccctg 2202

16U 200 PCT FINAL ST25

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 cctgcctcct cccaccctgc cagcctatga gtcccagag ggttggggca gtcccatgac 2442
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<400> 79

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Gly Val Arg Asp Trp Thr Leu Leu Gln Leu Val Val Ser Val Pro Phe
 35 40 45

Phe Leu Cys Phe Leu Tyr Ser Trp Trp Leu Ala Glu Ser Ala Arg Trp
 50 55 60

Leu Leu Thr Thr Gly Arg Leu Asp Trp Gly Leu Gln Glu Leu Trp Arg
 65 70 75 80

Val Ala Ala Ile Asn Gly Lys Gly Ala Val Gln Asp Thr Leu Thr Pro
 85 90 95

Glu Val Leu Leu Ser Ala Met Arg Glu Glu Leu Ser Met Gly Gln Pro
 100 105 110

Pro Ala Ser Leu Gly Thr Leu Leu Arg Met Pro Gly Leu Arg Phe Arg
 115 120 125

Thr Cys Ile Ser Thr Leu Cys Trp Phe Ala Phe Gly Phe Thr Phe Phe
 130 135 140

Gly Leu Ala Leu Asp Leu Gln Ala Leu Gly Ser Asn Ile Phe Leu Leu
 145 150 155 160

Gln Met Phe Ile Gly Val Val Asp Ile Pro Ala Lys Met Gly Ala Leu
 165 170 175

Leu Leu Leu Ser His Leu Gly Arg Arg Pro Thr Leu Ala Ala Ser Leu
 180 185 190

Leu Leu Ala Gly Leu Cys Ile Leu Ala Asn Thr Leu Val Pro His Glu
 195 200 205

Met Gly Ala Leu Arg Ser Ala Leu Ala Val Leu Gly Leu Gly Gly Val
 210 215 220

Gly Ala Ala Phe Thr Cys Ile Thr Ile Tyr Ser Ser Glu Leu Phe Pro
 225 230 235 240

16U 200 PCT FINAL.ST25

Thr Val Leu Arg Met Thr Ala Val Gly Leu Gly Gln Met Ala Ala Arg
245 250 255

Gly Gly Ala Ile Leu Gly Pro Leu Val Arg Leu Leu Gly Val His Gly
260 265 270

Pro Trp Leu Pro Leu Leu Val Tyr Gly Thr Val Pro Val Leu Ser Gly
275 280 285

Leu Ala Ala Leu Leu Leu Pro Glu Thr Gln Ser Leu Pro Leu Pro Asp
290 295 300

Thr Ile Gln Asp Val Gln Asn Gln Ala Val Lys Lys Ala Thr His Gly
305 310 315 320

Thr Leu Gly Asn Ser Val Leu Lys Ser Thr Gln Phe
325 330

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ggc tcc cag gat gcc ctg gcc ccc ttg cct cca cct gct ccc cag aat 99
Gly Ser Gln Asp Ala Leu Ala Pro Leu Pro Pro Pro Ala Pro Gln Asn
15 20 25 30

ccc tcc acc cac tct tgg gac cct ttg tgt gga tct ctg cct tgg ggc 147
Pro Ser Thr His Ser Trp Asp Pro Leu Cys Gly Ser Leu Pro Trp Gly
35 40 45

ctc agc tgt ctt ctg gct ctg cag cat gtc ttg gtc atg gct tct ctg 195
Leu Ser Cys Leu Leu Ala Leu Gln His Val Leu Val Met Ala Ser Leu
50 55 60

ctc tgt gtc tcc cac ctg ctc ctg ctt tgc agt ctc tcc cca gga gga 243
Leu Cys Val Ser His Leu Leu Leu Leu Cys Ser Leu Ser Pro Gly Gly
65 70 75

ctc tct tac tcc cct tct cag ctc ctg gcc tcc agc ttc ttt tca tgt 291
Leu Ser Tyr Ser Pro Ser Gln Leu Leu Ala Ser Ser Phe Phe Ser Cys
80 85 90

ggt atg tct acc atc ctg caa act tgg atg ggc agc agg ctg cct ctt 339
Gly Met Ser Thr Ile Leu Gln Thr Trp Met Gly Ser Arg Leu Pro Leu
95 100 105 110

gtc cag gct cca tcc tta gag ttc ctt atc cct gct ctg gtg ctg acc 387
Val Gln Ala Pro Ser Leu Glu Phe Leu Ile Pro Ala Leu Val Leu Thr
115 120 125

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Ser Gln Lys Leu Pro Arg Ala Ile Gln Thr Pro Gly Asn Ser Ser Leu
130 135 140

atg ctg cac ctt tgt agg gga cct agc tgc cat ggc ctg ggg cac tgg 483
Met Leu His Leu Cys Arg Gly Pro Ser Cys His Gly Leu Gly His Trp
145 150 155

aac act tct ctc cag gag gtg tcc ggg gca gtg gta gta tct ggg ctg 531
Asn Thr Ser Leu Gln Glu Val Ser Gly Ala Val Val Val Ser Gly Leu

160 165 160 200 PCT FINAL.ST25
170

ctg cag ggc atg atg ggg ctg ctg ggg agt ccc ggc cac gtg ttc ccc 579
Leu Gln Gly Met Met Gly Leu Leu Gly Ser Pro Gly His Val Phe Pro
175 180 185 190

cac tgt ggg ccc ctg gtg ctg gct ccc agc ctg gtt gtg gca ggg ctc 627
His Cys Gly Pro Leu Val Leu Ala Pro Ser Leu Val Val Ala Gly Leu
195 200 205

tct gcc cac agg gag gta gcc cag ttc tgc ttc aca cac tgg ggg ttg 675
Ser Ala His Arg Glu Val Ala Gln Phe Cys Phe Thr His Trp Gly Leu
210 215 220

gcc ttg ctg tac gtg agt cct gag agg cgt ggg atg gtg ccc agt ggg 723
Ala Leu Leu Tyr Val Ser Pro Glu Arg Arg Gly Met Val Pro Ser Gly
225 230 235

ggt gta tgg ggg gac tagggggagg cagaactgct ggtcctatca gattcagcag 778
Gly Val Trp Gly Asp
240

cgactggaat agggacatat ttatatattg gaatccaaga cttttccttg attcatctgg 838

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20 25 30

Thr His Ser Trp Asp Pro Leu Cys Gly Ser Leu Pro Trp Gly Leu Ser
35 40 45

Cys Leu Leu Ala Leu Gln His Val Leu Val Met Ala Ser Leu Leu Cys
50 55 60

Val Ser His Leu Leu Leu Leu Cys Ser Leu Ser Pro Gly Gly Leu Ser
65 70 75 80

Tyr Ser Pro Ser Gln Leu Leu Ala Ser Ser Phe Phe Ser Cys Gly Met
85 90 95

Ser Thr Ile Leu Gln Thr Trp Met Gly Ser Arg Leu Pro Leu Val Gln
100 105 110

Ala Pro Ser Leu Glu Phe Leu Ile Pro Ala Leu Val Leu Thr Ser Gln
115 120 125

Lys Leu Pro Arg Ala Ile Gln Thr Pro Gly Asn Ser Ser Leu Met Leu
130 135 140

His Leu Cys Arg Gly Pro Ser Cys His Gly Leu Gly His Trp Asn Thr
145 150 155 160

Ser Leu Gln Glu Val Ser Gly Ala Val Val Val Ser Gly Leu Leu Gln
165 170 175

Gly Met Met Gly Leu Leu Gly Ser Pro Gly His Val Phe Pro His Cys
180 185 190

Gly Pro Leu Val Leu Ala Pro Ser Leu Val Val Ala Gly Leu Ser Ala
195 200 205

His Arg Glu Val Ala Gln Phe Cys Phe Thr His Trp Gly Leu Ala Leu
210 215 220

Leu Tyr Val Ser Pro Glu Arg Arg Gly Met Val Pro Ser Gly Gly Val
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Trp Gly Asp

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160 200 PCT FINAL.ST25
Met Asp Arg Gly Glu Lys
1 5

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ctt att aat atc att ggt gca gga att ttt gtg tcc ccc aaa ggt gtg Leu Ile Asn Ile Ile Gly Ala Gly Ile Phe Val Ser Pro Lys Gly Val 25 30 35	212
ttg gca tac tct tgc atg aac gtg gga gtc tcc ctg tgc gtt tgg gct Leu Ala Tyr Ser Cys Met Asn Val Gly Val Ser Leu Cys Val Trp Ala 40 45 50	260
ggc tgt gcc ata ctg gcc atg aca tca act ctt tgc tct gca gag ata Gly Cys Ala Ile Leu Ala Met Thr Ser Thr Leu Cys Ser Ala Glu Ile 55 60 65 70	308
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tac ttt ggc tcc acg gtt gct ttt ttg aat ctc tgg aca tcc ttg ttt Tyr Phe Gly Ser Thr Val Ala Phe Leu Asn Leu Trp Thr Ser Leu Phe 90 95 100	404
ctg ggg tca ggg gta gtt gct ggc caa gct ctg ctc ctt gct gag tac Leu Gly Ser Gly Val Val Ala Gly Gln Ala Leu Leu Leu Ala Glu Tyr 105 110 115	452
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aaa tgt ctg gca ttg gcc atg ttg tgg att gta gga att ctg act tct Lys Cys Leu Ala Leu Ala Met Leu Trp Ile Val Gly Ile Leu Thr Ser 135 140 145 150	548
cgt ggt gtg aaa gaa gtg act tgg ctt cag ata gct agc tca gtg ctg Arg Gly Val Lys Glu Val Thr Trp Leu Gln Ile Ala Ser Ser Val Leu 155 160 165	596
aaa gtg tcc ata ctt agc ttc att tcc cta act gga gta gtg ttc ctg Lys Val Ser Ile Leu Ser Phe Ile Ser Leu Thr Gly Val Val Phe Leu 170 175 180	644
ata aga ggg aaa aag gag aat gta gaa cga ttt cag aat gct ttt gat Ile Arg Gly Lys Lys Glu Asn Val Glu Arg Phe Gln Asn Ala Phe Asp 185 190 195	692
gct gaa ctt cca gat atc tct cac ctt ata caa gcc atc ttc caa gga Ala Glu Leu Pro Asp Ile Ser His Leu Ile Gln Ala Ile Phe Gln Gly 200 205 210	740
tat ttt gca tat tca ggc ggg gca tgc ttt aca ctt ata gca ggg gag Tyr Phe Ala Tyr Ser Gly Gly Ala Cys Phe Thr Leu Ile Ala Gly Glu 215 220 225 230	788
ctg aag aag ccc aga aca aca att ccc aaa tgc ata ttt act gcg tta Leu Lys Lys Pro Arg Thr Thr Ile Pro Lys Cys Ile Phe Thr Ala Leu 235 240 245	836
cct ctg gtg act gta gtt tat tta ctg gtt aac att tcc tat ctg act Pro Leu Val Thr Val Val Tyr Leu Leu Val Asn Ile Ser Tyr Leu Thr 250 255 260	884
gtt ctg aca ccc agg gaa att ctc tct tca gat gct gta gct atc aca Val Leu Thr Pro Arg Glu Ile Leu Ser Ser Asp Ala Val Ala Ile Thr 265 270 275	932
tgg gct gat cga gct ttt ccc tca tta gca tgg att atg cct ttt gct Trp Ala Asp Arg Ala Phe Pro Ser Leu Ala Trp Ile Met Pro Phe Ala 280 285 290	980
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160 200 PCT FINAL.ST25

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 315 320 325

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 Phe Asn Thr Leu Asn Ser His Ser Ser Pro Phe Thr Ala Val Leu Leu
 330 335 340

ctt gtc act ttg gga tcc ctt gca att atc tta aca agt cta att gat 1172
 Leu Val Thr Leu Gly Ser Leu Ala Ile Ile Leu Thr Ser Leu Ile Asp
 345 350 355

ttg ata aac tat att ttt ttc acg ggt tca tta tgg tct ata tta tta 1220
 Leu Ile Asn Tyr Ile Phe Phe Thr Gly Ser Leu Trp Ser Ile Leu Leu
 360 365 370

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cct tat aag gtg ttt ttg tca ttt cca tta gca aca ata gtc atc gac 1316
 Pro Tyr Lys Val Phe Leu Ser Phe Pro Leu Ala Thr Ile Val Ile Asp
 395 400 405

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Leu Cys Ser Ala Glu Ile Ser Ile Ser Phe Pro Cys Ser Gly Ala Gln
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Cys Ile Phe Thr Ala Leu Pro Leu Val Thr Val Val Tyr Leu Leu Val
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Asn Ile Ser Tyr Leu Thr Val Leu Thr Pro Arg Glu Ile Leu Ser Ser
 260 265 270

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Ile Ser Ile Phe Lys Ser Ser Arg Pro Ile Tyr Leu Ala Ser Gln Glu
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Gly Gln Leu Pro Leu Leu Phe Asn Thr Leu Asn Ser His Ser Ser Pro
 325 330 335

Phe Thr Ala Val Leu Leu Leu Val Thr Leu Gly Ser Leu Ala Ile Ile
 340 345 350

Leu Thr Ser Leu Ile Asp Leu Ile Asn Tyr Ile Phe Phe Thr Gly Ser
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Leu Trp Ser Ile Leu Leu Met Ile Gly Ile Leu Arg Arg Arg Tyr Gln
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Glu Pro Asn Leu Ser Ile Pro Tyr Lys Val Phe Leu Ser Phe Pro Leu
 385 390 395 400

160 200 PCT FINAL.ST25

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Ser Pro Asn Val His Tyr Val Tyr Val Leu Leu Leu Val Leu Ser Gly
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 Tyr Cys Thr Leu Val Cys Ile
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 35 40 45

Ser Phe Gly Pro Val Gly Leu Ser Leu Thr Ala Ser Phe Met Ser Ala
 50 55 60

Val Thr Val Leu Gly Thr Pro Ser Glu Val Tyr Arg Phe Gly Ala Ser
 65 70 75 80

Phe Leu Val Phe Phe Ile Ala Tyr Leu Phe Val Ile Leu Leu Thr Ser
 85 90 95

Glu Leu Phe Leu Pro Val Phe Tyr Arg Ser Gly Ile Thr Ser Thr Tyr
 100 105 110

Glu Tyr Leu Gln Leu Arg Phe Asn Lys Pro Val Arg Tyr Ala Ala Thr
 115 120 125

Val Ile Tyr Ile Val Gln Thr Ile Leu Tyr Thr Gly Val Val Val Tyr
 130 135 140

Ala Pro Ala Leu Ala Leu Asn Gln Val Thr Gly Phe Asp Leu Trp Gly
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Val Thr Arg Cys Ile Ser Ile Phe Phe Val Glu Phe Gln Thr Tyr Phe
 65 70 75 80

Thr Gln Asp Tyr Ala Gln Thr Ala Trp Ile His Ser Ile Val Asp Cys
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Val Thr Met Leu Cys Ala Pro Leu Gly Ser Val Val Ser Asn His Leu
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Ser Cys Gln Val Gly Ile Met Leu Gly Gly Leu Leu Ala Ser Thr Gly
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160 200 PCT FINAL.ST25
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Val Pro Tyr Ala Leu Ser Val Gly Val Ser His Gln Gln Ala Ala Phe
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16U 200 PCT FINAL.ST25

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Page 59

16U 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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Page 66

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160 200 PCT FINAL.ST25

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160 200 PCT FINAL.ST25

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160 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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160 200 PCT FINAL.ST25

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Glu Ala Phe Lys Pro Val Cys Tyr Lys Pro Gln Phe Met Ser His Ile
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Phe Ser Ser Thr Gln Pro Ser Pro Pro Tyr Tyr Pro Gly Leu Val Leu
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Pro Asp Thr Asp Pro Glu Glu Ala Asn Ser Gly Gln Gln Asn Ile Lys
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Glu Gln Gln Tyr Arg Val Ser Leu Gly Asn Asn Thr Gly Ser Pro Leu
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Cys Ser Thr Glu Val Asn Phe Gly Ser Arg Gln Gln Gly Lys Leu Asn
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Arg Thr Thr Arg Glu Ala Trp Lys Glu Ala Ser Arg Trp Asp Leu Pro
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Ala Leu Gly Pro Ser Gly His Pro Leu Gln Leu Lys Val Thr Phe Ala
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Asn Gln Ile Leu Asp Ile Pro Gln Pro Gln Val Gly Trp Arg Ser Met
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Phe Pro Arg Gly Ala Glu Ala Gln Asp Trp His Leu Asp Met Gln Leu
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Thr Gly Lys Val Val Leu Ser Ala Ala Ala Leu Leu Leu Val Thr Val
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Ala Tyr Arg Leu Tyr Lys Ser Arg Pro Ala Pro Ala Gln Arg Trp Gly
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Gly Asn Gly Gln Ala Glu Ala Lys Glu Glu Ala Glu Gly Ser Gly Gln
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Pro Ala Val Gln Glu Ala Ser Pro Gly Val Leu Leu Arg Gly Pro Arg
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Glu Asn Pro Arg Gly Pro Tyr Val Leu Val Thr Gly Ala Thr Ser Thr
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Gly Ser Asp Ser Glu Gln Val Pro Pro Cys Cys Pro Ser Gln Glu Thr
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Arg Thr Ala Val Gly Ser Asn Pro Asp Pro Pro His Phe Pro Arg Leu
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Gly Ser Cys Ala Gly Gly Glu Pro Ser Pro Trp Gln Asp Ser Lys Pro
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Arg Glu His Pro Gly Leu Gly Gln Leu Glu Pro Pro His Cys His Tyr
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Phe Ile Gln Lys Ala Glu Gly Val Glu Pro Arg Leu Lys Gly Lys Val
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Trp Pro Ser Thr Arg Gly Phe Ser Arg Lys Glu Ser Leu Leu Gln Ile
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Ile Pro Leu Thr Pro Ala Ser Ala Pro Gln Val Arg Leu Asp Leu Gly
740 745 750

Asn Cys Tyr Glu Val Leu Thr Leu Ala Lys Arg Gln Asn Leu Glu Ala
755 760 765

Leu Lys Glu Ala Ala Tyr Lys Val Met Ser Glu Asn Tyr Leu Gln Val
770 775 780

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785 790 795 800

Leu Ile Leu Gln Arg Arg Leu Arg Gly Arg Gln Tyr Leu Val Val Ala
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Asp Val Cys Pro Lys Glu Asp Ser Gly Gly Leu Cys Cys Tyr Asp Asp
820 825 830

Glu Gln Asp Val Trp Arg Pro Leu Ala Arg Met Pro Pro Glu Ala Val
835 840 845

Ser Arg Gly Cys Ala Ile Cys Ser Leu Phe Asn Tyr Leu Phe Val Val
850 855 860

Ser Gly Cys Gln Gly Pro Gly His Gln Pro Ser Ser Arg Val Phe Cys
865 870 875 880

Tyr Asn Pro Leu Thr Gly Ile Trp Ser Glu Val Cys Pro Leu Asn Gln
885 890 895

Ala Arg Pro His Cys Arg Leu Val Ala Leu Asp Gly His Leu Tyr Ala
900 905 910

16U 200 PCT FINAL.ST25

Ile Gly Gly Glu Cys Leu Asn Ser Val Glu Arg Tyr Asp Pro Arg Leu
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Asp Arg Trp Asp Phe Ala Pro Pro Leu Pro Ser Asp Thr Phe Ala Leu
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Ala His Thr Ala Thr Val Arg Ala Lys Glu Ile Phe Val Thr Gly Gly
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Ser Leu Arg Phe Leu Leu Phe Arg Phe Ser Ala Gln Glu Gln Arg Trp
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Pro Val Ser Thr Glu Ala Ala Gly Ala Gln Ala Val Gly Leu Val
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Gly Arg Ser Arg Thr Gly Thr Lys Asp Glu Lys Glu Val Gly Met
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Phe Leu Pro Lys Ala Glu Gly Pro Gly Ser Gln Leu Gln Lys Leu Leu			
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Leu His Met Leu Gln Gln Lys Arg Ile Leu Glu Ser Pro Leu Leu Arg			
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Ala Ser Lys Glu Asn Asp Leu Ser Val Leu Arg Gln Leu Leu Leu Asp			
	55	60	65
tgc acc tgt gac gtt cga caa aga gga gcc ctg ggg gag acg gcg ctg			598
Cys Thr Cys Asp Val Arg Gln Arg Gly Ala Leu Gly Glu Thr Ala Leu			
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cac ata gca gcc ctc tat gac aac ttg gag gcg gcc ttg gtg ctg atg			646
His Ile Ala Ala Leu Tyr Asp Asn Leu Glu Ala Ala Leu Val Leu Met			
85	90	95	
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Glu Ala Ala Pro Glu Leu Val Phe Glu Pro Thr Thr Cys Glu Ala Phe			
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Ala Gly Gln Thr Ala Leu His Ile Ala Val Val Asn Gln Asn Val Asn			
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Gly Asn Thr Val Leu His Ile Leu Ile Leu Gln Pro Asn Lys Thr Phe			
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16U 200 PCT FINAL.ST25

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50 55 60

16U 200 PCT FINAL.ST25

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 65 70 75 80
 Thr Ala Leu His Ile Ala Ala Leu Tyr Asp Asn Leu Glu Ala Ala Leu
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 Val Leu Met Glu Ala Ala Pro Glu Leu Val Phe Glu Pro Thr Thr Cys
 100 105 110
 Glu Ala Phe Ala Gly Gln Thr Ala Leu His Ile Ala Val Val Asn Gln
 115 120 125
 Asn Val Asn Leu Val Arg Ala Leu Leu Thr Arg Arg Ala Ser Val Ser
 130 135 140
 Ala Arg Ala Thr Gly Thr Ala Phe Arg Arg Ser Pro Arg Asn Leu Ile
 145 150 155 160
 Tyr Phe Gly Glu His Pro Leu Ser Phe Ala Ala Cys Val Asn Ser Glu
 165 170 175
 Glu Ile Val Arg Leu Leu Ile Glu His Gly Ala Asp Ile Arg Ala Gln
 180 185 190
 Asp Ser Leu Gly Asn Thr Val Leu His Ile Leu Ile Leu Gln Pro Asn
 195 200 205
 Lys Thr Phe Ala Cys Gln Met Tyr Asn Leu Leu Leu Ser Tyr Asp Gly
 210 215 220
 His Gly Asp His Leu Gln Pro Leu Asp Leu Val Pro Asn His Gln Gly
 225 230 235 240
 Leu Thr Pro Phe Lys Leu Ala Gly Val Glu Gly Asn Thr Val Met Phe
 245 250 255
 Gln His Leu Met Gln Lys Arg Arg His Ile Gln Trp Thr Tyr Gly Pro
 260 265 270
 Leu Thr Ser Ile Leu Tyr Asp Leu Thr Glu Ile Asp Ser Trp Gly Glu
 275 280 285
 Glu Leu Ser Phe Leu Glu Leu Val Val Ser Ser Asp Lys Arg Glu Ala
 290 295 300
 Arg Gln Ile Leu Glu Gln Thr Pro Val Lys Glu Leu Val Ser Phe Lys
 305 310 315 320
 Trp Asn Lys Tyr Gly Arg Pro Tyr Phe Cys Ile Leu Ala Ala Leu Tyr
 325 330 335
 Leu Leu Tyr Met Ile Cys Phe Thr Thr Cys Cys Val Tyr Arg Pro Leu
 340 345 350
 Lys Phe Arg Gly Gly Asn Arg Thr His Ser Arg Asp Ile Thr Ile Leu
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 Gln Gln Lys Leu Leu Gln Glu Ala Tyr Glu Thr Arg Glu Asp Ile Ile
 370 375 380

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Arg Leu Val Gly Glu Leu Val Ser Ile Val Gly Ala Val Ile Ile Leu
 385 390 395 400

Leu Leu Glu Ile Pro Asp Ile Phe Arg Val Gly Ala Ser Arg Tyr Phe
 405 410 415

Gly Lys Thr Ile Leu Gly Gly Pro Phe His Val Ile Ile Ile Thr Tyr
 420 425 430

Ala Ser Leu Val Leu Val Thr Met Val Met Arg Leu Thr Asn Thr Asn
 435 440 445

Gly Glu Val Val Pro Met Ser Phe Ala Leu Val Leu Gly Trp Cys Ser
 450 455 460

Val Met Tyr Phe Thr Arg Gly Phe Gln Met Leu Gly Pro Phe Thr Ile
 465 470 475 480

Met Ile Gln Lys Met Ile Phe Gly Asp Leu Met Arg Phe Cys Trp Leu
 485 490 495

Met Ala Val Val Ile Leu Gly Phe Ala Ser Ala Phe Tyr Ile Ile Phe
 500 505 510

Gln Thr Glu Asp Pro Thr Ser Leu Gly Gln Phe Tyr Asp Tyr Pro Met
 515 520 525

Ala Leu Phe Thr Thr Phe Glu Leu Phe Leu Thr Val Ile Asp Ala Pro
 530 535 540

Ala Asn Tyr Asp Val Asp Leu Pro Phe Met Phe Ser Ile Val Asn Phe
 545 550 555 560

Ala Phe Ala Ile Ile Ala Thr Leu Leu Met Leu Asn Leu Phe Ile Ala
 565 570 575

Met Met Gly Asp Thr His Trp Arg Val Ala Gln Glu Arg Asp Glu Leu
 580 585 590

Trp Arg Ala Gln Val Val Ala Thr Thr Val Met Leu Glu Arg Lys Leu
 595 600 605

Pro Arg Cys Leu Trp Pro Arg Ser Gly Ile Cys Gly Cys Glu Phe Gly
 610 615 620

Leu Gly Asp Arg Trp Phe Leu Arg Val Glu Asn His Asn Asp Gln Asn
 625 630 635 640

Pro Leu Arg Val Leu Arg Tyr Val Glu Val Phe Lys Asn Ser Asp Lys
 645 650 655

Glu Asp Asp Gln Glu His Pro Ser Glu Lys Gln Pro Ser Gly Ala Glu
 660 665 670

Ser Gly Thr Leu Ala Arg Ala Ser Leu Ala Leu Pro Thr Ser Ser Leu
 675 680 685

Ser Arg Thr Ala Ser Gln Ser Ser Ser His Arg Gly Trp Glu Ile Leu

16U 200 PCT FINAL.ST25
700

690

695

Arg Gln Asn Thr Leu Gly His Leu Asn Leu Gly Leu Asn Leu Ser Glu
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Gly Asp Gly Glu Glu Val Tyr His Phe
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gccgtgggc atg ggc ctg gta cgc agc gtg ggc gcc ttg gcc gtg gtg gcc 171
Met Gly Leu Val Arg Ser Val Gly Ala Leu Ala Val Val Ala
1 5 10
gcc att ttt ggc ctg gag ttc ctc atg gtg tcc cag ttg tgc gag gac 219
Ala Ile Phe Gly Leu Glu Phe Leu Met Val Ser Gln Leu Cys Glu Asp
15 20 25 30
aaa cac tca cag tgc aag tgg gtc atg ggt tcc atc ctc ctc ctg gtg 267
Lys His Ser Gln Cys Lys Trp Val Met Gly Ser Ile Leu Leu Leu Val
35 40 45
tct ttc gtc ctc tcc tcc ggc ggg ctc ctg ggt ttt gtg atc ctc ctc 315
Ser Phe Val Leu Ser Ser Gly Gly Leu Leu Gly Phe Val Ile Leu Leu
50 55 60
agg aac caa gtc aca ctc atc ggc ttc acc cta atg ttt tgg tgc gaa 363
Arg Asn Gln Val Thr Leu Ile Gly Phe Thr Leu Met Phe Trp Cys Glu
65 70 75
ttc act gcc tcc ttc ctc ctc ttc ctg aac gcc atc agc ggc ctt cac 411
Phe Thr Ala Ser Phe Leu Leu Phe Leu Asn Ala Ile Ser Gly Leu His
80 85 90
atc aac agc atc acc cat ccc tgg gaa tgaccgtgga aattttaggc 458
Ile Asn Ser Ile Thr His Pro Trp Glu
95 100
ccctccagg gacatcagat tccacaagaa aatatggtca aaatgggact ttccagcat 518
gtggcctctg gtggggctgg gttggacaag ggccttgaaa cggctgcctg ttgcccata 578
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 35 40 45

Val Leu Ser Ser Gly Gly Leu Leu Gly Phe Val Ile Leu Leu Arg Asn
 50 55 60

Gln Val Thr Leu Ile Gly Phe Thr Leu Met Phe Trp Cys Glu Phe Thr
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 85 90 95

Ser Ile Thr His Pro Trp Glu
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gtgatgtctc gagaatgagt gcggttg 27

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160 200 PCT FINAL.ST25

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tta act gaa caa gca gag ctt cag ctg ccc ctc ttc tgc ctc ttc tta 96
Leu Thr Glu Gln Ala Glu Leu Gln Leu Pro Leu Phe Cys Leu Phe Leu

20 25 30

gga att tac aca gtt act gtg gtg gga aac ctc agc atg atc tca att 144
Gly Ile Tyr Thr Val Thr Val Val Gly Asn Leu Ser Met Ile Ser Ile

35 40 45

att agg ctg aat cgt caa ctt cat acc ccc atg tac tat ttc ctg agt 192
Ile Arg Leu Asn Arg Gln Leu His Thr Pro Met Tyr Tyr Phe Leu Ser

50 55 60

agt ttg tct ttt tta gat ttc tgc tat tct tct gtc att acc cct aaa 240
Ser Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Val Ile Thr Pro Lys

65 70 75 80

atg cta tca ggg ttt tta tgc aga gat aga tcc atc tcc tat tct gga 288
Met Leu Ser Gly Phe Leu Cys Arg Asp Arg Ser Ile Ser Tyr Ser Gly

85 90 95

tgc atg att cag ctg ttt ttt ttc tgt gtt tgt gtt att tct gaa tgc 336
Cys Met Ile Gln Leu Phe Phe Phe Cys Val Cys Val Ile Ser Glu Cys

100 105 110

tac atg ctg gca gcc atg gcc tgc gat cgc tac gtg gcc atc tgc agc 384
Tyr Met Leu Ala Ala Met Ala Cys Asp Arg Tyr Val Ala Ile Cys Ser

115 120 125

cca ctg ctc tac agg gtc atc atg tcc cct agg gtc tgt tct ctg ctg 432
Pro Leu Leu Tyr Arg Val Ile Met Ser Pro Arg Val Cys Ser Leu Leu

130 135 140

gtg gct gct gtc ttc tca gta ggt ttc act gat gct gtg atc cat gga 480
Val Ala Ala Val Phe Ser Val Gly Phe Thr Asp Ala Val Ile His Gly

145 150 155 160

ggg tgt ata ctc agg ttg tct ttc tgt gga tca aac atc att aaa cat 528
Gly Cys Ile Leu Arg Leu Ser Phe Cys Gly Ser Asn Ile Ile Lys His

165 170 175

tat ttc tgt gac att gtc cct ctt att aaa ctc tcc tgc tcc agc act 576
Tyr Phe Cys Asp Ile Val Pro Leu Ile Lys Leu Ser Cys Ser Ser Thr

180 185 190

tat att gat gag ctt ttg att ttt gtc att ggt gga ttt aac atg gtg 624
Tyr Ile Asp Glu Leu Leu Ile Phe Val Ile Gly Gly Phe Asn Met Val

195 200 205

gcc aca agc cta aca atc att att tca tat gct ttt atc ctc acc agc 672
Ala Thr Ser Leu Thr Ile Ile Ile Ser Tyr Ala Phe Ile Leu Thr Ser

210 215 220

atc ctg cgc atc cac tct aaa aag ggc agg tgc aaa gcg ttt agc acc 720
Ile Leu Arg Ile His Ser Lys Lys Gly Arg Cys Lys Ala Phe Ser Thr

225 230 235 240

tgt agc tcc cac ctg aca gct gtt ctt atg ttt tat ggg tct ctg atg 768

16U 200 PCT FINAL.ST25
 Cys Ser Ser His Leu Thr Ala Val Leu Met Phe Tyr Gly Ser Leu Met
 245 250 255
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 Ser Met Tyr Leu Lys Pro Ala Ser Ser Ser Leu Thr Gln Glu Lys
 260 265 270
 gta tcc tca gta ttt tat acc act gtg att ctc atg ttg aat ccc ttg 864
 Val Ser Ser Val Phe Tyr Thr Thr Val Ile Leu Met Leu Asn Pro Leu
 275 280 285
 ata tat agt ctg agg aac aat gaa gta aga aat gct ctg atg aaa ctt 912
 Ile Tyr Ser Leu Arg Asn Asn Glu Val Arg Asn Ala Leu Met Lys Leu
 290 295 300
 tta aga aga aaa ata tct tta tct cca gga taa 945
 Leu Arg Arg Lys Ile Ser Leu Ser Pro Gly
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Gly Ile Tyr Thr Val Thr Val Val Gly Asn Leu Ser Met Ile Ser Ile
 35 40 45

Ile Arg Leu Asn Arg Gln Leu His Thr Pro Met Tyr Tyr Phe Leu Ser
 50 55 60

Ser Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Val Ile Thr Pro Lys
 65 70 75 80

Met Leu Ser Gly Phe Leu Cys Arg Asp Arg Ser Ile Ser Tyr Ser Gly
 85 90 95

Cys Met Ile Gln Leu Phe Phe Phe Cys Val Cys Val Ile Ser Glu Cys
 100 105 110

Tyr Met Leu Ala Ala Met Ala Cys Asp Arg Tyr Val Ala Ile Cys Ser
 115 120 125

Pro Leu Leu Tyr Arg Val Ile Met Ser Pro Arg Val Cys Ser Leu Leu
 130 135 140

Val Ala Ala Val Phe Ser Val Gly Phe Thr Asp Ala Val Ile His Gly
 145 150 155 160

Gly Cys Ile Leu Arg Leu Ser Phe Cys Gly Ser Asn Ile Ile Lys His
 165 170 175

Tyr Phe Cys Asp Ile Val Pro Leu Ile Lys Leu Ser Cys Ser Ser Thr
 180 185 190

Tyr Ile Asp Glu Leu Leu Ile Phe Val Ile Gly Gly Phe Asn Met Val
 195 200 205

16U 200 PCT FINAL.ST25

Ala Thr Ser Leu Thr Ile Ile Ile Ser Tyr Ala Phe Ile Leu Thr Ser
 210 215 220

Ile Leu Arg Ile His Ser Lys Lys Gly Arg Cys Lys Ala Phe Ser Thr
 225 230 235 240

Cys Ser Ser His Leu Thr Ala Val Leu Met Phe Tyr Gly Ser Leu Met
 245 250 255

Ser Met Tyr Leu Lys Pro Ala Ser Ser Ser Ser Leu Thr Gln Glu Lys
 260 265 270

Val Ser Ser Val Phe Tyr Thr Thr Val Ile Leu Met Leu Asn Pro Leu
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Leu Arg Arg Lys Ile Ser Leu Ser Pro Gly
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34

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36

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ctc tct cag gtt tgg gag ctt cgg ttt gtt ttc ttc act gtt ttc tct 96
 Leu Ser Gln Val Trp Glu Leu Arg Phe Val Phe Phe Thr Val Phe Ser
 20 25 30

gct gtg tat ttt atg act gta gtg gga aac ctt ctt att gtg gtc ata 144
 Ala Val Tyr Phe Met Thr Val Val Gly Asn Leu Leu Ile Val Val Ile
 35 40 45

gtg acc tcc gac cca cac ctg cac aca acc atg tat ttt ctc ttg ggc 192
 Val Thr Ser Asp Pro His Leu His Thr Thr Met Tyr Phe Leu Leu Gly
 50 55 60

aat ctt tct ttc ctg gac ttt tgc tac tct tcc atc aca gca cct agg 240
 Asn Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Ile Thr Ala Pro Arg
 65 70 75 80

atg ctg gtt gac ttg ctc tca ggc aac cct acc att tcc ttt ggt gga 288
 Met Leu Val Asp Leu Leu Ser Gly Asn Pro Thr Ile Ser Phe Gly Gly
 85 90 95

tgc ctg act caa ctc ttc ttc ttc cac ttc att gga ggc atc aag atc 336
 Cys Leu Thr Gln Leu Phe Phe Phe His Phe Ile Gly Gly Ile Lys Ile
 100 105 110

ttc ctg ctg act gtc atg gcg tat gac cgc tac att gcc att tcc cag 384
 Phe Leu Leu Thr Val Met Ala Tyr Asp Arg Tyr Ile Ala Ile Ser Gln
 115 120 125

ccc ctg cac tac acg ctc att atg aat cag act gtc tgt gca ctc ctt 432
 Pro Leu His Tyr Thr Leu Ile Met Asn Gln Thr Val Cys Ala Leu Leu
 130 135 140

atg gca gcc tcc tgg gtg ggg ggc ttc atc cac tcc ata gta cag att 480
 Met Ala Ala Ser Trp Val Gly Gly Phe Ile His Ser Ile Val Gln Ile
 145 150 155 160

gca ttg act atc cag ctg cca ttc tgt ggg cct gac aag ctg gac aac 528
 Ala Leu Thr Ile Gln Leu Pro Phe Cys Gly Pro Asp Lys Leu Asp Asn
 165 170 175

ttt tat tgt gat gtg cct cag ctg atc aaa ttg gcc tgc aca gat acc 576
 Phe Tyr Cys Asp Val Pro Gln Leu Ile Lys Leu Ala Cys Thr Asp Thr
 180 185 190

16U 200 PCT FINAL.ST25

ttt gtc tta gag ctt tta atg gtg tct aac aat ggc ctg gtg acc ctg 624
 Phe Val Leu Glu Leu Leu Met Val Ser Asn Asn Gly Leu Val Thr Leu
 195 200 205

atg tgt ttt ctg gtg ctt ctg gga tgc tac aca gca ctg cta gtc atg 672
 Met Cys Phe Leu Val Leu Leu Gly Ser Tyr Thr Ala Leu Leu Val Met
 210 215 220

ctc cga agc cac tca cgg gag ggc cgc agc aag gcc ctg tct acc tgt 720
 Leu Arg Ser His Ser Arg Glu Gly Arg Ser Lys Ala Leu Ser Thr Cys
 225 230 235 240

gcc tct cac att gct gtg gtg acc tta atc ttt gtg cct tgc atc tac 768
 Ala Ser His Ile Ala Val Val Thr Leu Ile Phe Val Pro Cys Ile Tyr
 245 250 255

gtc tat aca agg cct ttt cgg aca ttc ccc atg gac aag gcc gtc tct 816
 Val Tyr Thr Arg Pro Phe Arg Thr Phe Pro Met Asp Lys Ala Val Ser
 260 265 270

gtg cta tac aca att gtc acc ccc atg ctg aat cct gcc atc tat acc 864
 Val Leu Tyr Thr Ile Val Thr Pro Met Leu Asn Pro Ala Ile Tyr Thr
 275 280 285

ctg aga aac aag gaa gtg atc atg gcc atg aag aag ctg tgg agg agg 912
 Leu Arg Asn Lys Glu Val Ile Met Ala Met Lys Lys Leu Trp Arg Arg
 290 295 300

aaa aag gac cct att ggt ccc ctg gag cac aga ccc tta cat tag 957
 Lys Lys Asp Pro Ile Gly Pro Leu Glu His Arg Pro Leu His
 305 310 315

<210> 163
 <211> 318
 <212> PRT
 <213> Homo sapiens

<400> 163

Met Asn Pro Ala Asn His Ser Gln Val Ala Gly Phe Val Leu Leu Gly
 1 5 10 15

Leu Ser Gln Val Trp Glu Leu Arg Phe Val Phe Phe Thr Val Phe Ser
 20 25 30

Ala Val Tyr Phe Met Thr Val Val Gly Asn Leu Leu Ile Val Val Ile
 35 40 45

Val Thr Ser Asp Pro His Leu His Thr Thr Met Tyr Phe Leu Leu Gly
 50 55 60

Asn Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Ile Thr Ala Pro Arg
 65 70 75 80

Met Leu Val Asp Leu Leu Ser Gly Asn Pro Thr Ile Ser Phe Gly Gly
 85 90 95

Cys Leu Thr Gln Leu Phe Phe Phe His Phe Ile Gly Gly Ile Lys Ile
 100 105 110

Phe Leu Leu Thr Val Met Ala Tyr Asp Arg Tyr Ile Ala Ile Ser Gln
 115 120 125

Pro Leu His Tyr Thr Leu Ile Met Asn Gln Thr Val Cys Ala Leu Leu
 130 135 140

Met Ala Ala Ser Trp Val Gly Gly Phe Ile His Ser Ile Val Gln Ile
 145 150 155 160

16U 200 PCT FINAL.ST25

Ala Leu Thr Ile Gln Leu Pro Phe Cys Gly Pro Asp Lys Leu Asp Asn
165 170 175

Phe Tyr Cys Asp Val Pro Gln Leu Ile Lys Leu Ala Cys Thr Asp Thr
180 185 190

Phe Val Leu Glu Leu Leu Met Val Ser Asn Asn Gly Leu Val Thr Leu
195 200 205

Met Cys Phe Leu Val Leu Leu Gly Ser Tyr Thr Ala Leu Leu Val Met
210 215 220

Leu Arg Ser His Ser Arg Glu Gly Arg Ser Lys Ala Leu Ser Thr Cys
225 230 235 240

Ala Ser His Ile Ala Val Val Thr Leu Ile Phe Val Pro Cys Ile Tyr
245 250 255

Val Tyr Thr Arg Pro Phe Arg Thr Phe Pro Met Asp Lys Ala Val Ser
260 265 270

Val Leu Tyr Thr Ile Val Thr Pro Met Leu Asn Pro Ala Ile Tyr Thr
275 280 285

Leu Arg Asn Lys Glu Val Ile Met Ala Met Lys Lys Leu Trp Arg Arg
290 295 300

Lys Lys Asp Pro Ile Gly Pro Leu Glu His Arg Pro Leu His
305 310 315

<210> 164
<211> 26
<212> DNA
<213> Homo sapiens

<400> 164
gaatccagca aatcattccc aggtgg 26

<210> 165
<211> 29
<212> DNA
<213> Homo sapiens

<400> 165
ctaagtgaag ggtctgtgct ccaggggac 29

<210> 166
<211> 50
<212> DNA
<213> Homo sapiens

<400> 166
cactaccctt ttaaagtga gggggcagtg atttcttttc ttttcttttt 50

<210> 167
<211> 972
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(972)
<223>

16U 200 PCT FINAL.ST25

<400> 167
 atg aac cct gaa aac tgg act cag gta aca agc ttt gtc ctt ctg ggt 48
 Met Asn Pro Glu Asn Trp Thr Gln Val Thr Ser Phe Val Leu Leu Gly
 1 5 10 15

ttc ccc agt agc cac ctc ata cag ttc ctg gtg ttc ctg ggg tta atg 96
 Phe Pro Ser Ser His Leu Ile Gln Phe Leu Val Phe Leu Gly Leu Met
 20 25 30

gtg acc tac att gta aca gcc aca ggc aag ctg cta att att gtg ctc 144
 Val Thr Tyr Ile Val Thr Ala Thr Gly Lys Leu Leu Ile Ile Val Leu
 35 40 45

agc tgg ata gac caa cgc ctg cac ata cag atg tac ttc ttc ctg cgg 192
 Ser Trp Ile Asp Gln Arg Leu His Ile Gln Met Tyr Phe Phe Leu Arg
 50 55 60

aat ttc tcc ttc ctg gag ctg ttg ctg gta act gtt gtg gtt ccc aag 240
 Asn Phe Ser Phe Leu Glu Leu Leu Val Thr Val Val Val Pro Lys
 65 70 75 80

atg ctt gtc gtc atc ctc acg ggg gat cac acc atc tca ttt gtc agc 288
 Met Leu Val Val Ile Leu Thr Gly Asp His Thr Ile Ser Phe Val Ser
 85 90 95

tgc atc atc cag tcc tac ctc tac ttc ttt cta ggc acc act gac ttc 336
 Cys Ile Ile Gln Ser Tyr Leu Tyr Phe Phe Leu Gly Thr Thr Asp Phe
 100 105 110

ttc ctc ttg gcc gtc atg tct ctg gat cgt tac ctg gca atc tgc cga 384
 Phe Leu Leu Ala Val Met Ser Leu Asp Arg Tyr Leu Ala Ile Cys Arg
 115 120 125

cca ctc cgc tat gag acc ctg atg aat ggc cat gtc tgt tcc caa cta 432
 Pro Leu Arg Tyr Glu Thr Leu Met Asn Gly His Val Cys Ser Gln Leu
 130 135 140

gtg ctg gcc tcc tgg cta gct gga ttc ctc tgg gtc ctt tgc ccc act 480
 Val Leu Ala Ser Trp Leu Ala Gly Phe Leu Trp Val Leu Cys Pro Thr
 145 150 155 160

gtc ctc atg gcc agc ctg cct ttc tgt ggc ccc aat ggt att gac cac 528
 Val Leu Met Ala Ser Leu Pro Phe Cys Gly Pro Asn Gly Ile Asp His
 165 170 175

ttc ttt cgt gac agt tgg ccc ttg ctc agg ctt tct tgt ggg gac acc 576
 Phe Phe Arg Asp Ser Trp Pro Leu Leu Arg Leu Ser Cys Gly Asp Thr
 180 185 190

cac ctg ctg aaa ctg gtg gct ttc atg ctc tct acg ttg gtg tta ctg 624
 His Leu Leu Lys Leu Val Ala Phe Met Leu Ser Thr Leu Val Leu Leu
 195 200 205

ggc tca ctg gct ctg acc tca gtt tcc tat gcc tgc att ctt gcc act 672
 Gly Ser Leu Ala Leu Thr Ser Val Ser Tyr Ala Cys Ile Leu Ala Thr
 210 215 220

gtt ctc agg gcc cct aca gct gct gag cga agg aaa gcg ttt tcc act 720
 Val Leu Arg Ala Pro Thr Ala Ala Glu Arg Lys Ala Phe Ser Thr
 225 230 235 240

tgc gcc tgc cat ctt aca gtg gtg gtc atc atc tat ggc agt tcc atc 768
 Cys Ala Ser His Leu Thr Val Val Val Ile Ile Tyr Gly Ser Ser Ile
 245 250 255

ttt ctc tac att cgt atg tca gag gct cag tcc aaa ctg ctc aac aaa 816
 Phe Leu Tyr Ile Arg Met Ser Glu Ala Gln Ser Lys Leu Leu Asn Lys
 260 265 270

ggc gcc tcc gtc ctg agc tgc atc atc aca ccc ctc ttg aac cca ttc 864
 Gly Ala Ser Val Leu Ser Cys Ile Ile Thr Pro Leu Leu Asn Pro Phe
 275 280 285

atc ttc act ctc cgc aat gac aag gtg cag caa gca ctg aga gaa gcc 912
 Ile Phe Thr Leu Arg Asn Asp Lys Val Gln Gln Ala Leu Arg Glu Ala
 290 295 300

ttg ggg tgg ccc agg ctc act gct gtg atg aaa ctg agg gtc aca agt 960
 Leu Gly Trp Pro Arg Leu Thr Ala Val Met Lys Leu Arg Val Thr Ser

16U 200 PCT FINAL.ST25
315 320

305 310

caa agg aaa tga
Gln Arg Lys

972

<210> 168
<211> 323
<212> PRT
<213> Homo sapiens

<400> 168

Met Asn Pro Glu Asn Trp Thr Gln Val Thr Ser Phe Val Leu Leu Gly
1 5 10 15

Phe Pro Ser Ser His Leu Ile Gln Phe Leu Val Phe Leu Gly Leu Met
20 25 30

Val Thr Tyr Ile Val Thr Ala Thr Gly Lys Leu Leu Ile Ile Val Leu
35 40 45

Ser Trp Ile Asp Gln Arg Leu His Ile Gln Met Tyr Phe Phe Leu Arg
50 55 60

Asn Phe Ser Phe Leu Glu Leu Leu Leu Val Thr Val Val Val Pro Lys
65 70 75 80

Met Leu Val Val Ile Leu Thr Gly Asp His Thr Ile Ser Phe Val Ser
85 90 95

Cys Ile Ile Gln Ser Tyr Leu Tyr Phe Phe Leu Gly Thr Thr Asp Phe
100 105 110

Phe Leu Leu Ala Val Met Ser Leu Asp Arg Tyr Leu Ala Ile Cys Arg
115 120 125

Pro Leu Arg Tyr Glu Thr Leu Met Asn Gly His Val Cys Ser Gln Leu
130 135 140

Val Leu Ala Ser Trp Leu Ala Gly Phe Leu Trp Val Leu Cys Pro Thr
145 150 155 160

Val Leu Met Ala Ser Leu Pro Phe Cys Gly Pro Asn Gly Ile Asp His
165 170 175

Phe Phe Arg Asp Ser Trp Pro Leu Leu Arg Leu Ser Cys Gly Asp Thr
180 185 190

His Leu Leu Lys Leu Val Ala Phe Met Leu Ser Thr Leu Val Leu Leu
195 200 205

Gly Ser Leu Ala Leu Thr Ser Val Ser Tyr Ala Cys Ile Leu Ala Thr
210 215 220

Val Leu Arg Ala Pro Thr Ala Ala Glu Arg Arg Lys Ala Phe Ser Thr
225 230 235 240

Cys Ala Ser His Leu Thr Val Val Val Ile Ile Tyr Gly Ser Ser Ile
245 250 255

Phe Leu Tyr Ile Arg Met Ser Glu Ala Gln Ser Lys Leu Leu Asn Lys

16U 200 PCT FINAL.ST25
270

260

265

Gly Ala Ser Val Leu Ser Cys Ile Ile Thr Pro Leu Leu Asn Pro Phe
275 280 285

Ile Phe Thr Leu Arg Asn Asp Lys Val Gln Gln Ala Leu Arg Glu Ala
290 295 300

Leu Gly Trp Pro Arg Leu Thr Ala Val Met Lys Leu Arg Val Thr Ser
305 310 315 320

Gln Arg Lys

<210> 169
<211> 25
<212> DNA
<213> Homo sapiens

<400> 169
tgtgctcagc tggatagacc aacgc

25

<210> 170
<211> 30
<212> DNA
<213> Homo sapiens

<400> 170
ctgagaacag tggcaagaat gcaggcatag

30

<210> 171
<211> 450
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(450)
<223>

<400> 171
atg gac ctt ccc cat gtc cca gct ctg gac gcc cca ctc ttt gga gtc
Met Asp Leu Pro His Val Pro Ala Leu Asp Ala Pro Leu Phe Gly Val
1 5 10 15

48

ttc ctg gtg gtt tat gtg ctt act gtg ctg ggg aac ctc ctc atc ctg
Phe Leu Val Val Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu
20 25 30

96

ctg gtg atc agg gtg tac tct cac ctc cac acc ccc aag tac tac ttc
Leu Val Ile Arg Val Tyr Ser His Leu His Thr Pro Lys Tyr Tyr Phe
35 40 45

144

ctc acc aat ctg tcc ttc att gac ttg tgg ttc ttc act gtc atg gtg
Leu Thr Asn Leu Ser Phe Ile Asp Leu Trp Phe Phe Thr Val Met Val
50 55 60

192

ccc aaa atg ccg agg acc ttg ttg tcc ctg tgt ggc aag gct gtg tcc
Pro Lys Met Pro Arg Thr Leu Leu Ser Leu Cys Gly Lys Ala Val Ser
65 70 75 80

240

ttc cac agt tgt atg acc caa ctc tat ttc ttc tac ttc ctg ggg agc
Phe His Ser Cys Met Thr Gln Leu Tyr Phe Phe Tyr Phe Leu Gly Ser
85 90 95

288

acc gag tgt ttg ctc tac acg gtc atg tcc tat gat cgc tat aga gga
Thr Glu Cys Leu Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Arg Gly
100 105 110

336

aat act cag cac ttc cca ggt agt gaa aac act ccc cac gaa gtg agc
Asn Thr Gln His Phe Pro Gly Ser Glu Asn Thr Pro His Glu Val Ser
115 120 125

384

16U 200 PCT FINAL.ST25

caa atg cta gtg gcc cgg ggg gca cac ggg ctc cca ctc atc atc ctg 432
 Gln Met Leu Val Ala Arg Gly Ala His Gly Leu Pro Leu Ile Ile Leu
 130 135 140

gca gat ctg agt ggg taa 450
 Ala Asp Leu Ser Gly
 145

<210> 172
 <211> 149
 <212> PRT
 <213> Homo sapiens

<400> 172

Met Asp Leu Pro His Val Pro Ala Leu Asp Ala Pro Leu Phe Gly Val
 1 5 10 15

Phe Leu Val Val Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu
 20 25 30

Leu Val Ile Arg Val Tyr Ser His Leu His Thr Pro Lys Tyr Tyr Phe
 35 40 45

Leu Thr Asn Leu Ser Phe Ile Asp Leu Trp Phe Phe Thr Val Met Val
 50 55 60

Pro Lys Met Pro Arg Thr Leu Leu Ser Leu Cys Gly Lys Ala Val Ser
 65 70 75 80

Phe His Ser Cys Met Thr Gln Leu Tyr Phe Phe Tyr Phe Leu Gly Ser
 85 90 95

Thr Glu Cys Leu Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Arg Gly
 100 105 110

Asn Thr Gln His Phe Pro Gly Ser Glu Asn Thr Pro His Glu Val Ser
 115 120 125

Gln Met Leu Val Ala Arg Gly Ala His Gly Leu Pro Leu Ile Ile Leu
 130 135 140

Ala Asp Leu Ser Gly
 145

<210> 173
 <211> 23
 <212> DNA
 <213> Homo sapiens

<400> 173

agctctggac gccccactct ttg 23

<210> 174
 <211> 27
 <212> DNA
 <213> Homo sapiens

<400> 174

accactcag atctgccagg atgatga 27

<210> 175
 <211> 936
 <212> DNA
 <213> Homo sapiens

16U 200 PCT FINAL.ST25

<220>

<221> CDS

<222> (1)..(936)

<223>

<400> 175

atg tcc aac gcc agc ctc gtg aca gca ttc atc ctc aca ggc ctt ccc	48
Met Ser Asn Ala Ser Leu Val Thr Ala Phe Ile Leu Thr Gly Leu Pro	
1 5 10 15	
cat gcc cca ggg ctg gac gcc ctc ctc ttt gga atc ttc ctg gtg gtt	96
His Ala Pro Gly Leu Asp Ala Leu Leu Phe Gly Ile Phe Leu Val Val	
20 25 30	
tac gtg ctc act gtg ctg ggg aac ctc ctc atc ctg ctg gtg atc agg	144
Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu Leu Val Ile Arg	
35 40 45	
gtg gat tct cac ctc cac acc ccc atg tac tac ttc ctc acc aac ctg	192
Val Asp Ser His Leu His Thr Pro Met Tyr Tyr Phe Leu Thr Asn Leu	
50 55 60	
tcc ttc att gac atg tgg ttc tcc act gtc acg gtg ccc aaa atg ctg	240
Ser Phe Ile Asp Met Trp Phe Ser Thr Val Thr Val Pro Lys Met Leu	
65 70 75 80	
atg acc ttg gtg tcc cca agc ggc agg gct atc tcc ttc cac agc tgc	288
Met Thr Leu Val Ser Pro Ser Gly Arg Ala Ile Ser Phe His Ser Cys	
85 90 95	
gtg gct cag ctc tat ttt ttc cac ttc ctg ggg agc acc gag tgt ttc	336
Val Ala Gln Leu Tyr Phe Phe His Phe Leu Gly Ser Thr Glu Cys Phe	
100 105 110	
ctc tac aca gtc atg tcc tat gat cgc tac ttg gcc atc agt tac ccg	384
Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Leu Ala Ile Ser Tyr Pro	
115 120 125	
ctc agg tac acc agc atg atg agt ggg agc agg tgt gcc ctc ctg gcc	432
Leu Arg Tyr Thr Ser Met Met Ser Gly Ser Arg Cys Ala Leu Leu Ala	
130 135 140	
acc ggc act tgg ctc agt ggc tct ctg cac tct gct gtc cag acc ata	480
Thr Gly Thr Trp Leu Ser Gly Ser Leu His Ser Ala Val Gln Thr Ile	
145 150 155 160	
ttg act ttc cat ttg ccc tac tgt gga ccc aac cag atc cag cac tac	528
Leu Thr Phe His Leu Pro Tyr Cys Gly Pro Asn Gln Ile Gln His Tyr	
165 170 175	
ttc tgt gac gca ccg ccc atc ctg aaa ctg gcc tgt gca gac acc tca	576
Phe Cys Asp Ala Pro Pro Ile Leu Lys Leu Ala Cys Ala Asp Thr Ser	
180 185 190	
gcc aac gtg atg gtc atc ttt gtg gac att ggg ata gtg gcc tca ggc	624
Ala Asn Val Met Val Ile Phe Val Asp Ile Gly Ile Val Ala Ser Gly	
195 200 205	
tgc ttt gtc ctg ata gtg ctg tcc tat gtg tcc atc gtc tgt tcc atc	672
Cys Phe Val Leu Ile Val Leu Ser Tyr Val Ser Ile Val Cys Ser Ile	
210 215 220	
ctg cgg atc cgc acc tca gat ggg agg cgc aga gcc ttt cag acc tgt	720
Leu Arg Ile Arg Thr Ser Asp Gly Arg Arg Ala Phe Gln Thr Cys	
225 230 235 240	
gcc tcc cac tgt att gtg gtc ctt tgc ttc ttt gtt ccc tgt gtt gtc	768
Ala Ser His Cys Ile Val Val Leu Cys Phe Phe Val Pro Cys Val Val	
245 250 255	
att tat ctg agg cca ggc tcc atg gat gcc atg gat gga gtt gtg gcc	816
Ile Tyr Leu Arg Pro Gly Ser Met Asp Ala Met Asp Gly Val Val Ala	
260 265 270	
att ttc tac act gtg ctg acg ccc ctt ctc aac cct gtt gtg tac acc	864
Ile Phe Tyr Thr Val Leu Thr Pro Leu Leu Asn Pro Val Val Tyr Thr	
275 280 285	

16U 200 PCT FINAL.ST25
 ctg aga aac aag gag gtg aag aaa gct gtg ttg aaa ctt aga gac aaa 912
 Leu Arg Asn Lys Glu Val Lys Lys Ala Val Leu Lys Leu Arg Asp Lys
 290 295 300

gta gca cat cct cag agg aaa taa 936
 Val Ala His Pro Gln Arg Lys
 305 310

<210> 176
 <211> 311
 <212> PRT
 <213> Homo sapiens

<400> 176

Met Ser Asn Ala Ser Leu Val Thr Ala Phe Ile Leu Thr Gly Leu Pro
 1 5 10 15

His Ala Pro Gly Leu Asp Ala Leu Leu Phe Gly Ile Phe Leu Val Val
 20 25 30

Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu Leu Val Ile Arg
 35 40 45

Val Asp Ser His Leu His Thr Pro Met Tyr Tyr Phe Leu Thr Asn Leu
 50 55 60

Ser Phe Ile Asp Met Trp Phe Ser Thr Val Thr Val Pro Lys Met Leu
 65 70 75 80

Met Thr Leu Val Ser Pro Ser Gly Arg Ala Ile Ser Phe His Ser Cys
 85 90 95

Val Ala Gln Leu Tyr Phe Phe His Phe Leu Gly Ser Thr Glu Cys Phe
 100 105 110

Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Leu Ala Ile Ser Tyr Pro
 115 120 125

Leu Arg Tyr Thr Ser Met Met Ser Gly Ser Arg Cys Ala Leu Leu Ala
 130 135 140

Thr Gly Thr Trp Leu Ser Gly Ser Leu His Ser Ala Val Gln Thr Ile
 145 150 155 160

Leu Thr Phe His Leu Pro Tyr Cys Gly Pro Asn Gln Ile Gln His Tyr
 165 170 175

Phe Cys Asp Ala Pro Pro Ile Leu Lys Leu Ala Cys Ala Asp Thr Ser
 180 185 190

Ala Asn Val Met Val Ile Phe Val Asp Ile Gly Ile Val Ala Ser Gly
 195 200 205

Cys Phe Val Leu Ile Val Leu Ser Tyr Val Ser Ile Val Cys Ser Ile
 210 215 220

Leu Arg Ile Arg Thr Ser Asp Gly Arg Arg Arg Ala Phe Gln Thr Cys
 225 230 235 240

Ala Ser His Cys Ile Val Val Leu Cys Phe Phe Val Pro Cys Val Val
 245 250 255

16U 200 PCT FINAL.ST25

Ile Tyr Leu Arg Pro Gly Ser Met Asp Ala Met Asp Gly Val Val Ala
 260 265 270

Ile Phe Tyr Thr Val Leu Thr Pro Leu Leu Asn Pro Val Val Tyr Thr
 275 280 285

Leu Arg Asn Lys Glu Val Lys Lys Ala Val Leu Lys Leu Arg Asp Lys
 290 295 300

Val Ala His Pro Gln Arg Lys
 305 310

<210> 177
 <211> 29
 <212> DNA
 <213> Homo sapiens

<400> 177
 caaccagatc cagcactact tctgtgacg 29

<210> 178
 <211> 33
 <212> DNA
 <213> Homo sapiens

<400> 178
 ttatttcctc tgaggatgtg ctactttgtc tct 33

<210> 179
 <211> 50
 <212> DNA
 <213> Homo sapiens

<400> 179
 taggagaagc cctttaaaag caggcaatag taaggacatc agtaacaata 50

<210> 180
 <211> 50
 <212> DNA
 <213> Homo sapiens

<400> 180
 gctgggtgct ctttatatcc ccagagggag agagaccaag ggtgagaaga 50

<210> 181
 <211> 921
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(921)
 <223>

<400> 181
 atg gtg act gag ttt ctt ctt ctc ggc ttc tcc cac ctg gcc gac ctc 48
 Met Val Thr Glu Phe Leu Leu Leu Gly Phe Ser His Leu Ala Asp Leu
 1 5 10 15

cag ggc ttg ctc ttc tct gtc ttt ctc act atc tac ctg ctg acc gtg 96
 Gln Gly Leu Leu Phe Ser Val Phe Leu Thr Ile Tyr Leu Leu Thr Val
 20 25 30

gca ggc aat ttc ctc att gtg gtg ctg gtc tcc act gat gct gcc ctc 144
 Ala Gly Asn Phe Leu Ile Val Val Leu Val Ser Thr Asp Ala Ala Leu
 35 40 45

cag tcc cct atg tac ttc ttc ctg cgc acc ctc tcg gcc ttg gag att 192
 Gln Ser Pro Met Tyr Phe Phe Leu Arg Thr Leu Ser Ala Leu Glu Ile
 50 55 60

16U 200 PCT FINAL.ST25

ggc tat acg tct gtc acg gtc ccc ctg cta ctt cac cac ctc ctt act 240
 Gly Tyr Thr Ser Val Thr Val Pro Leu Leu Leu His His Leu Leu Thr
 65 70 75 80

ggc cgg cgc cac atc tct cgc tct gga tgt gct ctc cag atg ttc ttc 288
 Gly Arg Arg His Ile Ser Arg Ser Gly Cys Ala Leu Gln Met Phe Phe
 85 90 95

ttc ctc ttc ttt ggc gcc acg gag tgc tgc ctc ctg gca gcc atg gcc 336
 Phe Leu Phe Phe Gly Ala Thr Glu Cys Cys Leu Leu Ala Ala Met Ala
 100 105 110

tat gac cgc tat gca gcc atc tgt gaa ccc ctc cgc tac cca ctg ctg 384
 Tyr Asp Arg Tyr Ala Ala Ile Cys Glu Pro Leu Arg Tyr Pro Leu Leu
 115 120 125

ctg agc cac cgg gtg tgt cta cag cta gct ggg tcg gcg tgg gcc tgt 432
 Leu Ser His Arg Val Cys Leu Gln Leu Ala Gly Ser Ala Trp Ala Cys
 130 135 140

ggg gtg ctg gtg ggg ctg ggc cac acc cct ttc atc ttc tct ttg ccc 480
 Gly Val Leu Val Gly Leu Gly His Thr Pro Phe Ile Phe Ser Leu Pro
 145 150 155 160

ttc tgc ggc ccc aat acc atc ccg cag ttc ttc tgt gag atc cag cct 528
 Phe Cys Gly Pro Asn Thr Ile Pro Gln Phe Phe Cys Glu Ile Gln Pro
 165 170 175

gtc ctg cag ctg gta tgt gga gac acc tcg ctt aat gaa ctg cag att 576
 Val Leu Gln Leu Val Cys Gly Asp Thr Ser Leu Asn Glu Leu Gln Ile
 180 185 190

atc ctg gca aca gcc ctc ctc atc ctc tgc ccc ttt ggc ctc atc ctg 624
 Ile Leu Ala Thr Ala Leu Leu Ile Leu Cys Pro Phe Gly Leu Ile Leu
 195 200 205

ggc tcc tac ggg cgt atc ctc gtt acc atc ttc cgg atc cca tct gtt 672
 Gly Ser Tyr Gly Arg Ile Leu Val Thr Ile Arg Ile Pro Ser Val
 210 215 220

gcg ggc cgc cgc aag gcc ttc tcc acc tgc tcc tcc cac ctg atc gtg 720
 Ala Gly Arg Arg Lys Ala Phe Ser Thr Cys Ser Ser His Leu Ile Val
 225 230 235 240

gtc tcc ctc ttc tat ggc acc gca ctc ttt atc tat att cgc cct aag 768
 Val Ser Leu Phe Tyr Gly Thr Ala Leu Phe Ile Tyr Ile Arg Pro Lys
 245 250 255

gcc agc tac gat ccg gcc act gac cct ctg gtg tcc ctc ttc tat gct 816
 Ala Ser Tyr Asp Pro Ala Thr Asp Pro Leu Val Ser Leu Phe Tyr Ala
 260 265 270

gtg gtc acc ccc atc ctc aac ccc atc atc tac agc ctg cgg aac aca 864
 Val Val Thr Pro Ile Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn Thr
 275 280 285

gag gtc aaa gct gcc cta aag aga acc atc cag aaa acg gtg cct atg 912
 Glu Val Lys Ala Ala Leu Lys Arg Thr Ile Gln Lys Thr Val Pro Met
 290 295 300

gag att tga 921
 Glu Ile
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<400> 182

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160 200 PCT FINAL.ST25

Ala Gly Asn Phe Leu Ile Val Val Leu Val Ser Thr Asp Ala Ala Leu
 35 40 45
 Gln Ser Pro Met Tyr Phe Phe Leu Arg Thr Leu Ser Ala Leu Glu Ile
 50 55 60
 Gly Tyr Thr Ser Val Thr Val Pro Leu Leu Leu His His Leu Leu Thr
 65 70 75 80
 Gly Arg Arg His Ile Ser Arg Ser Gly Cys Ala Leu Gln Met Phe Phe
 85 90 95
 Phe Leu Phe Phe Gly Ala Thr Glu Cys Cys Leu Leu Ala Ala Met Ala
 100 105 110
 Tyr Asp Arg Tyr Ala Ala Ile Cys Glu Pro Leu Arg Tyr Pro Leu Leu
 115 120 125
 Leu Ser His Arg Val Cys Leu Gln Leu Ala Gly Ser Ala Trp Ala Cys
 130 135 140
 Gly Val Leu Val Gly Leu Gly His Thr Pro Phe Ile Phe Ser Leu Pro
 145 150 155 160
 Phe Cys Gly Pro Asn Thr Ile Pro Gln Phe Phe Cys Glu Ile Gln Pro
 165 170 175
 Val Leu Gln Leu Val Cys Gly Asp Thr Ser Leu Asn Glu Leu Gln Ile
 180 185 190
 Ile Leu Ala Thr Ala Leu Leu Ile Leu Cys Pro Phe Gly Leu Ile Leu
 195 200 205
 Gly Ser Tyr Gly Arg Ile Leu Val Thr Ile Phe Arg Ile Pro Ser Val
 210 215 220
 Ala Gly Arg Arg Lys Ala Phe Ser Thr Cys Ser Ser His Leu Ile Val
 225 230 235 240
 Val Ser Leu Phe Tyr Gly Thr Ala Leu Phe Ile Tyr Ile Arg Pro Lys
 245 250 255
 Ala Ser Tyr Asp Pro Ala Thr Asp Pro Leu Val Ser Leu Phe Tyr Ala
 260 265 270
 Val Val Thr Pro Ile Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn Thr
 275 280 285
 Glu Val Lys Ala Ala Leu Lys Arg Thr Ile Gln Lys Thr Val Pro Met
 290 295 300
 Glu Ile
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16U 200 PCT FINAL.ST25

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<210> 185
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 ttt ggt gtc caa cac gaa ttt cag cat gtc ctt ttc att gta ctt ctt 96
 Phe Gly Val Gln His Glu Phe Gln His Val Leu Phe Ile Val Leu Leu
 20 25 30
 ctt atc tat gtg acc tcc ctg ata gga aat att gga atg atc tta ctc 144
 Leu Ile Tyr Val Thr Ser Leu Ile Gly Asn Ile Gly Met Ile Leu Leu
 35 40 45
 atc aag acc gat tcc aga ctt caa aca ccc atg tac ttt ttt cca caa 192
 Ile Lys Thr Asp Ser Arg Leu Gln Thr Pro Met Tyr Phe Phe Pro Gln
 50 55 60
 cat ttg gct ttt gtt gat atc tgt tat act tct gct atc act ccc aag 240
 His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys
 65 70 75 80
 atg ctc caa agc ttc aca gaa gaa aat aat ttg ata aca ttt cgg ggc 288
 Met Leu Gln Ser Phe Thr Glu Glu Asn Asn Leu Ile Thr Phe Arg Gly
 85 90 95
 tgt gtg ata caa ttc tta gtt tat gca aca ttt gca acc agt gac tgt 336
 Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
 100 105 110
 tac ctc cta gct att atg gca atg gat tgt tat gtt gcc atc tgt aag 384
 Tyr Leu Leu Ala Ile Met Ala Met Asp Cys Tyr Val Ala Ile Cys Lys
 115 120 125
 ccc ctt cgc tat ccc atg atc atg tcc caa aca gtc tac atc caa ctc 432
 Pro Leu Arg Tyr Pro Met Ile Met Ser Gln Thr Val Tyr Ile Gln Leu
 130 135 140
 gta gct ggc tca tat att ata ggc tca ata aat gcc tct gta cat aca 480
 Val Ala Gly Ser Tyr Ile Ile Gly Ser Ile Asn Ala Ser Val His Thr
 145 150 155 160
 ggt ttt aca ttt tca ctg tcc ttc tgc aag tct aat aaa atc aat cac 528
 Gly Phe Thr Phe Ser Leu Ser Phe Cys Lys Ser Asn Lys Ile Asn His
 165 170 175
 ttt ttc tgt gat ggt ctc cca att ctt gcc ctt tca tgc tcc aac att 576
 Phe Phe Cys Asp Gly Leu Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile
 180 185 190
 gac atc aac atc att cta gat gtt gtc ttt gtg gga ttt gac ttg atg 624
 Asp Ile Asn Ile Ile Leu Asp Val Val Phe Val Gly Phe Asp Leu Met
 195 200 205
 ttc act gag ttg gtc atc atc ttt tcc tac atc tac att atg gtc acc 672
 Phe Thr Glu Leu Val Ile Ile Phe Ser Tyr Ile Tyr Ile Met Val Thr
 210 215 220

16U 200 PCT FINAL.ST25

atc ctg aag atg tct tct act gct ggg agg aaa aaa tcc ttc tcc aca 720
 ile leu lys met ser ser thr ala gly arg lys lys ser phe ser thr
 225 230 235 240
 tgt gcc tcc cac ctg aca gca gta acc att ttc tat ggg aca ctc tct 768
 cys ala ser his leu thr ala val thr ile phe tyr gly thr leu ser
 245 250 255
 tac atg tac tta cag cct cag tct aat aat tct cag gag aat atg aaa 816
 tyr met tyr leu gln pro gln ser asn asn ser gln glu asn met lys
 260 265 270
 gta gcc tct ata ttt tat ggc act gtt att ccc atg ttg aat cct tta 864
 val ala ser ile phe tyr gly thr val ile pro met leu asn pro leu
 275 280 285
 atc tat agc ttg aga aat aag gaa gga aaa taa 897
 ile tyr ser leu arg asn lys glu gly lys
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 Leu Ile Tyr Val Thr Ser Leu Ile Gly Asn Ile Gly Met Ile Leu Leu
 35 40 45
 Ile Lys Thr Asp Ser Arg Leu Gln Thr Pro Met Tyr Phe Phe Pro Gln
 50 55 60
 His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys
 65 70 75 80
 Met Leu Gln Ser Phe Thr Glu Glu Asn Asn Leu Ile Thr Phe Arg Gly
 85 90 95
 Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
 100 105 110
 Tyr Leu Leu Ala Ile Met Ala Met Asp Cys Tyr Val Ala Ile Cys Lys
 115 120 125
 Pro Leu Arg Tyr Pro Met Ile Met Ser Gln Thr Val Tyr Ile Gln Leu
 130 135 140
 Val Ala Gly Ser Tyr Ile Ile Gly Ser Ile Asn Ala Ser Val His Thr
 145 150 155 160
 Gly Phe Thr Phe Ser Leu Ser Phe Cys Lys Ser Asn Lys Ile Asn His
 165 170 175
 Phe Phe Cys Asp Gly Leu Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile
 180 185 190
 Asp Ile Asn Ile Ile Leu Asp Val Val Phe Val Gly Phe Asp Leu Met
 195 200 205

16U 200 PCT FINAL.ST25

Phe Thr Glu Leu Val Ile Ile Phe Ser Tyr Ile Tyr Ile Met Val Thr
210 215 220

Ile Leu Lys Met Ser Ser Thr Ala Gly Arg Lys Lys Ser Phe Ser Thr
225 230 235 240

Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser
245 250 255

Tyr Met Tyr Leu Gln Pro Gln Ser Asn Asn Ser Gln Glu Asn Met Lys
260 265 270

Val Ala Ser Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu
275 280 285

Ile Tyr Ser Leu Arg Asn Lys Glu Gly Lys
290 295

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ttt ggt gcc cag cat gag ttt tgg tgt atc ctc ttc att gta ttc ctt 96
Phe Gly Ala Gln His Glu Phe Trp Cys Ile Leu Phe Ile Val Phe Leu
20 25 30
ctc atc tat gtg acc tcc ata atg ggt aat agt gga ata atc tta ctc 144
Leu Ile Tyr Val Thr Ser Ile Met Gly Asn Ser Gly Ile Ile Leu Leu
35 40 45
atc aac aca gat tcc aga ttt caa aca ctc acg tac ttt ttt cta caa 192
Ile Asn Thr Asp Ser Arg Phe Gln Thr Leu Thr Tyr Phe Phe Leu Gln
50 55 60
cat ttg gct ttt gtt gat atc tgt tac act tct gct atc act ccc aag 240
His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys
65 70 75 80
atg ctc caa agc ttc aca gaa gaa aag aat ttg atg tta ttt cag ggc 288
Met Leu Gln Ser Phe Thr Glu Glu Lys Asn Leu Met Leu Phe Gln Gly
85 90 95
tgt gtg ata caa ttc tta gtt tat gca aca ttt gca acc agt gac tgt 336
Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
100 105 110
tat ctc ctg gct atg atg gca gtg gat cct tat gtt gcc atc tgt aag 384
Tyr Leu Leu Ala Met Met Ala Val Asp Pro Tyr Val Ala Ile Cys Lys
115 120 125
ccc ctt cac tat act gta atc atg tcc cga aca gtc tgc atc cgt ttg 432
Pro Leu His Tyr Thr Val Ile Met Ser Arg Thr Val Cys Ile Arg Leu
130 135 140
gta gct ggt tca tac atc atg ggc tca ata aat gcc tct gta caa aca 480
Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val Gln Thr
145 150 155 160
ggg ttt aca tgt tca ctg tcc ttc tgc aag tcc aat agc atc aat cac 528
Gly Phe Thr Cys Ser Leu Ser Phe Cys Lys Ser Asn Ser Ile Asn His

160 200 PCT FINAL.ST25

165

170

175

ttt ttc tgt gat gtt ccc cct att ctt gct ctt tca tgc tcc aat gtt 576
 Phe Phe Cys Asp Val Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Val
 180 185 190

gac atc aac atc atg cta ctt gtt gtc ttt gtg gga tct aac ttg ata 624
 Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Ser Asn Leu Ile
 195 200 205

ttc act ggg ttg gtc gtc atc ttt tcc tac atc tac atc atg gcc acc 672
 Phe Thr Gly Leu Val Val Ile Phe Ser Tyr Ile Tyr Ile Met Ala Thr
 210 215 220

atc ctg aaa atg tct tct agt gca gga agg aaa aaa tcc ttc tca aca 720
 Ile Leu Lys Met Ser Ser Ser Ala Gly Arg Lys Lys Ser Phe Ser Thr
 225 230 235 240

tgt gct tcc cac ctg acc gca gtc acc att ttc tat ggg aca ctc tct 768
 Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser
 245 250 255

tac atg tat ttg cag tct cat tct aat aat tcc cag gaa aat atg aaa 816
 Tyr Met Tyr Leu Gln Ser His Ser Asn Ser Gln Glu Asn Met Lys
 260 265 270

gtg gcc ttt ata ttt tat ggc aca gtt att ccc atg tta aat cct tta 864
 Val Ala Phe Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu
 275 280 285

atc tat agc ttg aga aat aag gaa gta aaa gaa gct tta aaa gtg ata 912
 Ile Tyr Ser Leu Arg Asn Lys Glu Val Lys Glu Ala Leu Lys Val Ile
 290 295 300

ggg aaa aag tta ttt taa 930
 Gly Lys Lys Leu Phe
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<210> 188
 <211> 309
 <212> PRT
 <213> Homo sapiens

<400> 188

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Leu Ile Tyr Val Thr Ser Ile Met Gly Asn Ser Gly Ile Ile Leu Leu
 35 40 45

Ile Asn Thr Asp Ser Arg Phe Gln Thr Leu Thr Tyr Phe Phe Leu Gln
 50 55 60

His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys
 65 70 75 80

Met Leu Gln Ser Phe Thr Glu Glu Lys Asn Leu Met Leu Phe Gln Gly
 85 90 95

Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
 100 105 110

Tyr Leu Leu Ala Met Met Ala Val Asp Pro Tyr Val Ala Ile Cys Lys
 115 120 125

Pro Leu His Tyr Thr Val Ile Met Ser Arg Thr Val Cys Ile Arg Leu

160 200 PCT FINAL.ST25

130

135

140

Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val Gln Thr
 145 150 155 160

Gly Phe Thr Cys Ser Leu Ser Phe Cys Lys Ser Asn Ser Ile Asn His
 165 170 175

Phe Phe Cys Asp Val Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Val
 180 185 190

Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Ser Asn Leu Ile
 195 200 205

Phe Thr Gly Leu Val Val Ile Phe Ser Tyr Ile Tyr Ile Met Ala Thr
 210 215 220

Ile Leu Lys Met Ser Ser Ser Ala Gly Arg Lys Lys Ser Phe Ser Thr
 225 230 235 240

Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser
 245 250 255

Tyr Met Tyr Leu Gln Ser His Ser Asn Asn Ser Gln Glu Asn Met Lys
 260 265 270

Val Ala Phe Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu
 275 280 285

Ile Tyr Ser Leu Arg Asn Lys Glu Val Lys Glu Ala Leu Lys Val Ile
 290 295 300

Gly Lys Lys Leu Phe
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 Met Leu Gln Ser Phe Thr Glu Glu Lys Asn Leu Ile Ser Phe Trp Gly
 1 5 10 15

tgc atg ata caa tta ttg gtt tat gca aca ttt gca acc agt gac tgt 96
 Cys Met Ile Gln Leu Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
 20 25 30

tat ctc ctg gct atg ata gca gtg gac cat tat gtt gca atc tgt aag 144
 Tyr Leu Leu Ala Met Ile Ala Val Asp His Tyr Val Ala Ile Cys Lys
 35 40 45

ccc ctt cac tat acc gta atc acg tcc caa aca gtc tgc atc cat ttg 192
 Pro Leu His Tyr Thr Val Ile Thr Ser Gln Thr Val Cys Ile His Leu
 50 55 60

gta gct ggt tca tac atc atg ggc tca ata aat gcc tct gta cat aca 240
 Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val His Thr
 65 70 75 80

ggc ttt gca ttt tca ctg tct ttc tgc aag tcc aat aac atc aac cac 288

160 200 PCT FINAL.ST25

Gly Phe Ala Phe Ser Leu Ser Phe Cys Lys Ser Asn Asn Ile Asn His
 85 90 95
 ttt ttc tgt gat ggt ccc cca att ctt gcc ctt tca tgc tcc aat att 336
 Phe Phe Cys Asp Gly Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile
 100 105 110
 gac atc aac atc atg cta ctt gtt gtc ttt gtg gga ttt aac ttg atg 384
 Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Phe Asn Leu Met
 115 120 125
 ttc act ggg ttg gag aat atg aaa gtg gcc tct ata ttt tat ggc act 432
 Phe Thr Gly Leu Glu Asn Met Lys Val Ala Ser Ile Phe Tyr Gly Thr
 130 135 140
 gtt att ccc atg ttg aat cct tta atc tat agc ttg aga aat aag gaa 480
 Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn Lys Glu
 145 150 155 160
 gta aaa gaa gct tta aaa ttg ata ggg aaa aag ttc ttt taa 522
 Val Lys Glu Ala Leu Lys Leu Ile Gly Lys Lys Phe Phe
 165 170

<210> 190
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 Tyr Leu Leu Ala Met Ile Ala Val Asp His Tyr Val Ala Ile Cys Lys
 35 40 45
 Pro Leu His Tyr Thr Val Ile Thr Ser Gln Thr Val Cys Ile His Leu
 50 55 60
 Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val His Thr
 65 70 75 80
 Gly Phe Ala Phe Ser Leu Ser Phe Cys Lys Ser Asn Asn Ile Asn His
 85 90 95
 Phe Phe Cys Asp Gly Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile
 100 105 110
 Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Phe Asn Leu Met
 115 120 125
 Phe Thr Gly Leu Glu Asn Met Lys Val Ala Ser Ile Phe Tyr Gly Thr
 130 135 140
 Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn Lys Glu
 145 150 155 160
 Val Lys Glu Ala Leu Lys Leu Ile Gly Lys Lys Phe Phe
 165 170

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<221> CDS

<222> (43)..(372)

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<400> 191

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 Met Ser Gln Arg
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ctc tgc att aag cta tta gtt agt tca tat gtc atg ggt ttc cta aat 102
 Leu Cys Ile Lys Leu Val Ser Ser Tyr Val Met Gly Phe Leu Asn
 5 10 15 20

gcc tct ata aac ata agt ttc act ttc tca ttg aac ttc tgc aaa tcc 150
 Ala Ser Ile Asn Ile Ser Phe Thr Phe Ser Leu Asn Phe Cys Lys Ser
 25 30 35

aaa aca att aat cac ttt ttc tgt gat gaa cct cca att att gcc cta 198
 Lys Thr Ile Asn His Phe Phe Cys Asp Glu Pro Pro Ile Ile Ala Leu
 40 45 50

cca tgc tcc aat att gac ctc aac atc atg tta tta aca gta ttt gtg 246
 Pro Cys Ser Asn Ile Asp Leu Asn Ile Met Leu Leu Thr Val Phe Val
 55 60 65

gga tta aat ttg atg tgc act gtg atg gtg gtc atc att tcc tgc ata 294
 Gly Leu Asn Leu Met Cys Thr Val Met Val Val Ile Ile Ser Cys Ile
 70 75 80

tat gtc ctg gtt gcc atc ctg agg ata tct tct gct gca ggg aag aaa 342
 Tyr Val Leu Val Ala Ile Leu Arg Ile Ser Ser Ala Ala Gly Lys Lys
 85 90 95 100

aaa gtc tct cta cat gtg cct ccc acc tga cagcagtcac cattttctat 392
 Lys Val Ser Leu His Val Pro Pro Thr
 105

ggggttctct cttacatgta tctatgccat cgtattaatg agtctcaaaa acaagaaaaa 452

gtggcctctg tgttttatgg cattattatt cccatgttaa acccctt 499

<210> 192

<211> 109

<212> PRT

<213> Homo sapiens

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Gly Phe Leu Asn Ala Ser Ile Asn Ile Ser Phe Thr Phe Ser Leu Asn
 20 25 30

Phe Cys Lys Ser Lys Thr Ile Asn His Phe Phe Cys Asp Glu Pro Pro
 35 40 45

Ile Ile Ala Leu Pro Cys Ser Asn Ile Asp Leu Asn Ile Met Leu Leu
 50 55 60

Thr Val Phe Val Gly Leu Asn Leu Met Cys Thr Val Met Val Val Ile
 65 70 75 80

Ile Ser Cys Ile Tyr Val Leu Val Ala Ile Leu Arg Ile Ser Ser Ala
 85 90 95

Ala Gly Lys Lys Lys Val Ser Leu His Val Pro Pro Thr
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160 200 PCT FINAL.ST25

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 <222> (1)..(681)
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<400> 193

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 Met Ala Tyr Asp Arg Tyr Met Ala Ile Ser Lys Pro Leu Leu Tyr Ser
 1 5 10 15

cgg gcc aca ttc cca gag tta tgt gcc agt ctt gtt gag gct tca cac 96
 Arg Ala Thr Phe Pro Glu Leu Cys Ala Ser Leu Val Glu Ala Ser His
 20 25 30

ctt ggc ggc ttt gta aac tca acc atc atc acc agt gag aca cct acc 144
 Leu Gly Gly Phe Val Asn Ser Thr Ile Ile Thr Ser Glu Thr Pro Thr
 35 40 45

ttg agc ttc tgt ggc agc aat atc att gat gat ttc ttc tgt gat ctg 192
 Leu Ser Phe Cys Gly Ser Asn Ile Ile Asp Asp Phe Phe Cys Asp Leu
 50 55 60

ccc cca ctt gta aag ttg gtg tgt gat gtg aag gag cgc tac cag gct 240
 Pro Pro Leu Val Lys Leu Val Cys Asp Val Lys Glu Arg Tyr Gln Ala
 65 70 75 80

gtg ctg cat ttt atg ctt gcc tcc aat cat cac tcc cac tgc act tat 288
 Val Leu His Phe Met Leu Ala Ser Asn His His Ser His Cys Thr Tyr
 85 90 95

tct tgc gtc cat ctc ttc atc att gca gcc atc tcg aag atc cgt tcc 336
 Ser Cys Val His Leu Phe Ile Ile Ala Ala Ile Ser Lys Ile Arg Ser
 100 105 110

att aag ggc cgc ctc cag gtc ttc tcc act tgt ggg tct ccc ctg acg 384
 Ile Lys Gly Arg Leu Gln Val Phe Ser Thr Cys Gly Ser Pro Leu Thr
 115 120 125

gct ctc acc ttg tac tat ggt gca atc ttc ttt att tac tcc caa cca 432
 Ala Leu Thr Leu Tyr Tyr Gly Ala Ile Phe Phe Ile Tyr Ser Gln Pro
 130 135 140

aga act agc tat gcc tta aaa atg gat aaa ttg ggg tca gtg ttc tat 480
 Arg Thr Ser Tyr Ala Leu Lys Met Asp Lys Leu Gly Ser Val Phe Tyr
 145 150 155 160

act gtg gtg att cca atg cta aac ccc ttg atc tat agc tta aga aat 528
 Thr Val Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn
 165 170 175

aag gat gtc aaa gat gcc ttg aag aaa atg tta gat aga ctt cag ttt 576
 Lys Asp Val Lys Asp Ala Leu Lys Lys Met Leu Asp Arg Leu Gln Phe
 180 185 190

ctt aaa gaa aaa tat tgt aga tat ggg ctg gcc tgt agt gag cgc tac 624
 Leu Lys Glu Lys Tyr Cys Arg Tyr Gly Leu Ala Cys Ser Glu Arg Tyr
 195 200 205

ctc ctg gct gcc atg ggt tat gac tgc tat gag gca atc tcc aag ccc 672
 Leu Leu Ala Ala Met Gly Tyr Asp Cys Tyr Glu Ala Ile Ser Lys Pro
 210 215 220

ctg ctt taa 681
 Leu Leu
 225

<210> 194
 <211> 226
 <212> PRT
 <213> Homo sapiens

<400> 194

16U 200 PCT FINAL.ST25
Met Ala Tyr Asp Arg Tyr Met Ala Ile Ser Lys Pro Leu Leu Tyr Ser
1 5 10 15
Arg Ala Thr Phe Pro Glu Leu Cys Ala Ser Leu Val Glu Ala Ser His
20 25 30
Leu Gly Gly Phe Val Asn Ser Thr Ile Ile Thr Ser Glu Thr Pro Thr
35 40 45
Leu Ser Phe Cys Gly Ser Asn Ile Ile Asp Asp Phe Phe Cys Asp Leu
50 55 60
Pro Pro Leu Val Lys Leu Val Cys Asp Val Lys Glu Arg Tyr Gln Ala
65 70 75 80
Val Leu His Phe Met Leu Ala Ser Asn His His Ser His Cys Thr Tyr
85 90 95
Ser Cys Val His Leu Phe Ile Ile Ala Ala Ile Ser Lys Ile Arg Ser
100 105 110
Ile Lys Gly Arg Leu Gln Val Phe Ser Thr Cys Gly Ser Pro Leu Thr
115 120 125
Ala Leu Thr Leu Tyr Tyr Gly Ala Ile Phe Phe Ile Tyr Ser Gln Pro
130 135 140
Arg Thr Ser Tyr Ala Leu Lys Met Asp Lys Leu Gly Ser Val Phe Tyr
145 150 155 160
Thr Val Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn
165 170 175
Lys Asp Val Lys Asp Ala Leu Lys Lys Met Leu Asp Arg Leu Gln Phe
180 185 190
Leu Lys Glu Lys Tyr Cys Arg Tyr Gly Leu Ala Cys Ser Glu Arg Tyr
195 200 205
Leu Leu Ala Ala Met Gly Tyr Asp Cys Tyr Glu Ala Ile Ser Lys Pro
210 215 220
Leu Leu
225

<210> 195
<211> 1095
<212> DNA
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<222> (1)..(1095)
<223>

<400> 195
atg gcc tct gag acc ttc aac act gaa gac cca gcc ggg ttg atg cac
Met Ala Ser Glu Thr Phe Asn Thr Glu Asp Pro Ala Gly Leu Met His
1 5 10 15
tcg gat gcc ggc acc agc tgc ccc gtc ctt tgc aca tgc cgt aac cag
Ser Asp Ala Gly Thr Ser Cys Pro Val Leu Cys Thr Cys Arg Asn Gln
20 25 30

48

96

16U 200 PCT FINAL.ST25

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Ser Gly Leu Pro Glu Glu Ser Glu Pro Glu Ser Trp Thr Gly Gln Arg
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260 265 270

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Ser Phe Pro Gly Tyr Leu Thr Leu Pro Gly Phe Cys Val Thr Asp Ser
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16U 200 PCT FINAL.ST25

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 50 55 60

Val Pro Pro Gly Tyr Leu Thr Cys Tyr Met Glu Leu Gln Val Leu Asp
 65 70 75 80

Leu His Asn Asn Ser Leu Met Glu Leu Pro Arg Gly Leu Phe Leu His
 85 90 95

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Val Pro Ala Asp Met Phe Gln Glu Ala His Gly Leu Val His Ile Asp
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Phe Leu Ser Leu Glu Ala Leu Glu Gly Leu Pro Gly Leu Val Thr Leu
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Gln Ile Gly Gly Asn Pro Trp Val Cys Gly Cys Thr Met Glu Pro Leu
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Ser Gly Leu Pro Glu Glu Ser Glu Pro Glu Ser Trp Thr Gly Gln Arg
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Ser Tyr Glu Asn Leu Ala Phe Leu Lys Leu Lys Ala Leu Ser Ser Val
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Asn Phe Gly His Arg Gln Ala Val Val Gly Gly Leu Ser Asn Pro Leu
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Phe Met Tyr Leu Ile Thr Val Leu Gly Asn Leu Glu Met Ile Ile Leu
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Ile Leu Met Asp His Gln Leu His Ala Pro Met Tyr Phe Leu Leu Ser
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His Leu Ala Phe Met Asp Val Cys Tyr Ser Ser Ile Thr Val Pro Gln
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Cys Ala Ala Gln Phe Phe Leu Phe Thr Phe Phe Gly Ser Ile Asp Cys
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Tyr Leu Leu Ala Leu Met Ala Tyr Asp Arg Tyr Leu Ala Val Cys Gln
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180 185 190

16U 200 PCT FINAL.ST25

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 Ala Ser Met Val Val Ile Leu Val Ser Tyr Leu Phe Ile Ile Val Ala
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 225 230 235 240
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 His Leu Ala Phe Met Asp Val Cys Tyr Ser Ser Ile Thr Val Pro Gln
 65 70 75 80
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 Cys Ala Ala Gln Phe Phe Leu Phe Thr Phe Phe Gly Ser Ile Asp Cys
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 Tyr Leu Leu Ala Leu Met Ala Tyr Asp Arg Tyr Leu Ala Val Cys Gln
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 Pro Leu Leu Tyr Val Thr Ile Leu Thr Gln Gln Ala Arg Leu Ser Leu
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 145 150 155 160

16U 200 PCT FINAL.ST25

Val Ser Ala Phe Thr Leu Ser Phe Cys Gly Thr Ser Glu Ile Asp Phe
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Ile Phe Cys Asp Leu Pro Pro Leu Leu Lys Leu Thr Cys Gly Glu Ser
180 185 190

Tyr Thr Gln Glu Val Leu Ile Ile Met Phe Ala Ile Phe Val Ile Pro
195 200 205

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210 215 220

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225 230 235 240

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Cys Leu Asp Cys Lys Leu His Thr Pro Met Tyr Phe Phe Leu Ser His
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85 90 95

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160 200 PCT FINAL.ST25
110

100 105 110

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leu arg tyr asn ser leu met ser trp arg val cys thr val leu ala
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val ala ser trp val phe ser phe leu leu ala leu val pro leu val
145 150 155 160

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leu ile leu ser leu pro phe cys gly pro his glu ile asn his phe
165 170 175

ttc tgt gaa atc ctg tct gtc ctc aag ttg gcc tgt gct gac acc tgg 576
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180 185 190

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195 200 205

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225 230 235 240

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245 250 255

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260 265 270

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275 280 285

tat agc cta agg aat gca gag gtc aag ggc gcc ctg agg agg gca ctg 912
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arg lys glu arg leu thr
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Phe Tyr Thr Leu Thr Leu Leu Gly Asn Gly Val Ile Phe Gly Ile Ile
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Cys Leu Asp Cys Lys Leu His Thr Pro Met Tyr Phe Phe Leu Ser His
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Leu Ala Ile Val Asp Ile Ser Tyr Ala Ser Asn Tyr Val Pro Lys Met

Page 124

16U 200 PCT FINAL.ST25

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Ile Ile Tyr Leu Ser Thr Leu Leu Gly Asn Gly Phe Met Ile Phe Leu	35 40 45	
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Cys Leu Ala Gln Thr Ser Val Ser Leu Ala Leu Ala Thr Ala Glu Cys	100 105 110	
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Leu Leu Leu Ala Ala Met Ala Tyr Asp Arg Val Val Ala Ile Ser Asn	115 120 125	
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Pro Leu Arg Tyr Ser Val Val Met Asn Gly Pro Val Cys Val Cys Leu	130 135 140	
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Ala Cys Glu Ile Leu Ser Leu Ile Lys Leu Thr Cys Ser Asp Thr Ser	180 185 190	
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Met Tyr Met Lys Thr Gln Ser Lys Ser Tyr Pro Asp Gln Asp Lys Phe	260 265 270	
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Ala Cys Glu Ile Leu Ser Leu Ile Lys Leu Thr Cys Ser Asp Thr Ser
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Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly Leu Leu Thr Asp
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cag ctc tcc agc cct tct cgg ccc aca cag aag acc ctg tgc agc ctg 240
Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys Thr Leu Cys Ser Leu
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Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val
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Met Leu Ile Thr Phe Asp Arg Tyr Leu Ala Ile Lys Gln Pro Phe Arg
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Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly
115 120 125
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Leu Trp Leu Val Ser Tyr Leu Ile Gly Phe Leu Pro Leu Gly Ile Pro
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Arg Thr Val Ser Val Leu Ile Gly Ser Phe Ala Leu Ser Trp Thr Pro
225 230 235 240
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16U 200 PCT FINAL.ST25

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245 250 255

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260 265 270

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Gln Leu Tyr His Met Ala Leu Gly Val Lys Lys Val Leu Thr Ser Phe
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Leu Pro Leu Thr Asp Asp Ala Pro Pro Gly Ala Thr Glu Glu Pro Ala
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Lys Lys Val Gln Asp Val His Ala Val Glu Ile Ser Ala Phe Arg Cys
50 55 60

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Gly Phe Ile Gly Pro Lys Gly Gln Arg Ile Phe Leu Ile Leu Arg Gly
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Val Leu Gly Ser Thr Ala Met Met Leu Ile Tyr Tyr Ala Tyr Gln Thr
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115 120 125

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180 185 190

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195 200 205

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245 250 255

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260 265 270

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275 280 285

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Gly Phe Ile Gly Pro Lys Gly Gln Arg Ile Phe Leu Ile Leu Arg Gly

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 130 135 140
 Asp Ala Leu Phe Thr Val Phe Thr Ile Thr Gly Val Ile Leu Ile Val
 145 150 155 160
 Arg Pro Pro Phe Leu Phe Gly Ser Asp Thr Ser Gly Met Glu Glu Ser
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 Tyr Ser Gly His Leu Lys Gly Thr Phe Ala Ala Ile Gly Ser Ala Val
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 225 230 235 240
 Gly Leu Asp Arg Leu Phe Leu Ile Phe Ile Gly Leu Phe Gly Leu Gly
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 Gly Gln Ile Phe Ile Thr Lys Ala Leu Gln Ile Glu Lys Ala Gly Pro
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 Val Ala Ile Met Lys Thr Met Asp Val Val Phe Ala Phe Ile Phe Gln
 275 280 285
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 35 40 45

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 Ile Gly Val Ala Gln Leu Ala Cys Ala Asp Ile Ser Ile Asn Ile Trp
 165 170 175

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 180 185 190

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 245 250 255

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 Asn Leu Tyr Val Ile Ile Pro Pro Ala Leu Asn Ser Ile Val Tyr Arg
 260 265 270

ata aag acc aag caa atc cag aac aga atc ctt ttg ctc ttt ccc aag 864
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Met Ala Phe Asp Arg Tyr Met Ala Ile Cys Ser Pro Leu Arg Tyr Thr
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115 120 125
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Ile Gly Val Ala Gln Leu Ala Cys Ala Asp Ile Ser Ile Asn Ile Trp
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Cys Gly Phe Cys Val Pro Ile Met Thr Val Met Thr Asp Val Ile Leu
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195 200 205
Ser Gln Asp Ala Arg Gln Lys Ala Leu Cys Ser Cys Gly Ser His Val
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Cys Val Ile Leu Ile Phe Tyr Ile Pro Ala Phe Phe Ser Ile Leu Ala
225 230 235 240
His Cys Phe Gly His Asn Val Pro His Thr Phe His Ile Met Phe Ala
245 250 255
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16U 200 PCT FINAL.ST25

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Gln Pro Trp Gln Thr Arg Asp Val Ser Cys Ser Asp Arg Asn Pro Tyr
195 200 205

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Gln Ala Thr Gln Ala Gly Leu Arg Ser Arg Pro Ala Gln Leu His Val
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120 125 130 135

160 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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160 200 PCT FINAL.ST25

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160 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25
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16U 200 PCT FINAL.ST25

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35 40 45

Ser Leu Gln Arg Phe Thr Ala Pro Thr Ser Gln Phe Tyr His Leu Phe
50 55 60

Leu His Gly Asn Ser Leu Thr Arg Leu Phe Pro Asn Glu Phe Ala Asn
65 70 75 80

Phe Tyr Asn Ala Val Ser Leu His Met Glu Asn Asn Gly Leu His Glu
85 90 95

Ile Val Pro Gly Ala Phe Leu Gly Leu Gln Leu Val Lys Arg Leu His
100 105 110

Ile Asn Asn Asn Lys Ile Lys Ser Phe Arg Lys Gln Thr Phe Leu Gly
115 120 125

Leu Asp Asp Leu Glu Tyr Leu Gln Ala Asp Phe Asn Leu Leu Arg Asp
130 135 140

Ile Asp Pro Gly Ala Phe Gln Asp Leu Asn Lys Leu Glu Val Leu Ile
145 150 155 160

Leu Asn Asp Asn Leu Ile Ser Thr Leu Pro Ala Asn Val Phe Gln Tyr
165 170 175

Val Pro Ile Thr His Leu Asp Leu Arg Gly Asn Arg Leu Lys Thr Leu
180 185 190

Pro Tyr Glu Glu Val Leu Glu Gln Ile Pro Gly Ile Ala Glu Ile Leu
195 200 205

Leu Glu Asp Asn Pro Trp Asp Cys Thr Cys Asp Leu Leu Ser Leu Lys
210 215 220

160 200 PCT FINAL.ST25

Glu Trp Leu Glu Asn Ile Pro Lys Asn Ala Leu Ile Gly Arg Val Val
 225 230 235 240

Cys Glu Ala Pro Thr Arg Leu Gln Gly Lys Asp Leu Asn Glu Thr Thr
 245 250 255

Glu Gln Asp Leu Cys Pro Leu Lys Asn Arg Val Asp Ser Ser Leu Pro
 260 265 270

Ala Pro Pro Ala Gln Glu Glu Thr Phe Ala Pro Gly Pro Leu Pro Thr
 275 280 285

Pro Phe Lys Thr Asn Gly Gln Glu Asp His Ala Thr Pro Gly Ser Ala
 290 295 300

Pro Asn Gly Gly Thr Lys Ile Pro Gly Asn Trp Gln Ile Lys Ile Arg
 305 310 315 320

Pro Thr Ala Ala Ile Ala Thr Gly Ser Ser Arg Asn Lys Pro Leu Ala
 325 330 335

Asn Ser Leu Pro Cys Pro Gly Gly Cys Ser Cys Asp His Ile Pro Gly
 340 345 350

Ser Gly Leu Lys Met Asn Cys Asn Asn Arg Asn Val Ser Ser Leu Ala
 355 360 365

Asp Leu Lys Pro Lys Leu Ser Asn Val Gln Glu Leu Phe Leu Arg Asp
 370 375 380

Asn Lys Ile His Ser Ile Arg Lys Ser His Phe Val Asp Tyr Lys Asn
 385 390 395 400

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 420 425 430

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Asn Leu Leu Arg Ser Leu Pro Val Asp Val Phe Ala Gly Val Ser Leu
 485 490 495

Ser Lys Leu Ser Leu His Asn Asn Tyr Phe Met Tyr Leu Pro Val Ala
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Gly Val Leu Asp Gln Leu Thr Ser Ile Ile Gln Ile Asp Leu His Gly
 515 520 525

Asn Pro Trp Glu Cys Ser Cys Thr Ile Val Pro Phe Lys Gln Trp Ala
 530 535 540

16U 200 PCT FINAL-ST25

Glu Arg Leu Gly Ser Glu Val Leu Met Ser Asp Leu Lys Cys Glu Thr
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Pro Val Asn Phe Phe Arg Lys Asp Phe Met Leu Leu Ser Asn Asp Glu
565 570 575

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580 585 590

Ser Lys Asn Ser Thr Gly Leu Ala Glu Thr Gly Thr His Ser Asn Ser
595 600 605

Tyr Leu Asp Thr Ser Arg Val Ser Ile Ser Val Leu Val Pro Gly Leu
610 615 620

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Phe Ile Leu Arg Asn Arg Lys Arg Ser Lys Arg Arg Asp Ala Asn Ser
645 650 655

Ser Ala Ser Glu Ile Asn Ser Leu Gln Thr Val Cys Asp Ser Ser Tyr
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Arg Thr Lys Ile Met Ile Gly Ile Gly Ser Ser Leu Leu Val Ala Ala
10 15 20

atg gtg ctc cta agt gtt gtg ttc tgt ctt tac ttc aaa gta gct aag 148
Met Val Leu Leu Ser Val Val Phe Cys Leu Tyr Phe Lys Val Ala Lys
25 30 35

gca cta aaa gct gca aag gac cct gat gct gtg gct gta aaa aat cac 196
Ala Leu Lys Ala Ala Lys Asp Pro Asp Ala Val Ala Val Lys Asn His
40 45 50 55

aac cca gac aag gtg tgt tgg gcc acg aac agc cag gcc aaa gcc acc 244
Asn Pro Asp Lys Val Cys Trp Ala Thr Asn Ser Gln Ala Lys Ala Thr
60 65 70

acc atg gag tct tgt cca tct ctc cag tgc tgt gaa ggt tgt aga atg 292
Thr Met Glu Ser Cys Pro Ser Leu Gln Cys Cys Glu Gly Cys Arg Met
75 80 85

cat gcc agt tct gat tcc ctg cca cct tgc tgt tgt gac ata aat gag 340
His Ala Ser Ser Asp Ser Leu Pro Cys Cys Cys Asp Ile Asn Glu
90 95 100

16U 200 PCT FINAL.ST25

ggc ctc tgacttggga aagctgggca caaaaatctt catgagcaat attctttctt 396
Gly Leu
105

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20 25 30

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35 40 45

Ala Val Ala Val Lys Asn His Asn Pro Asp Lys Val Cys Trp Ala Thr
50 55 60

Asn Ser Gln Ala Lys Ala Thr Thr Met Glu Ser Cys Pro Ser Leu Gln
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atg acc acc aac ttg gat ctg aag gta tcc atg ctc agc ttc atc tca 227
Met Thr Thr Asn Leu Asp Leu Lys Val Ser Met Leu Ser Phe Ile Ser
1 5 10 15

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Ala Thr Cys Leu Leu Leu Cys Leu Asn Leu Phe Val Ala Gln Val His
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tgg cat act agg gat gcc atg gag tca gat ctc cta tgg acc tat tat 323
Trp His Thr Arg Asp Ala Met Glu Ser Asp Leu Leu Trp Thr Tyr Tyr
35 40 45

ctt aac tgg tgc agt gac atc ttt tac atg ttt gct ggg atc atc tct 371
Leu Asn Trp Cys Ser Asp Ile Phe Tyr Met Phe Ala Gly Ile Ile Ser
50 55 60

ctt ctc aac tac tta act tcc aga tcg cct gcc tgt gat gaa aac gtc 419

16U 200 PCT FINAL.ST25
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 65 70 75 80
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 Thr Val Ile Pro Thr Glu Arg Ser Arg Leu Gly Val Gly Pro Val Thr
 85 90 95
 aca gta tca cct gct aaa gat gaa ggg cca agg tct gag atg gaa tct 515
 Thr Val Ser Pro Ala Lys Asp Glu Gly Pro Arg Ser Glu Met Glu Ser
 100 105 110
 cta agt gtg aga gag aaa aat tta cca aag tca gga ctg tgg tgg 560
 Leu Ser Val Arg Glu Lys Asn Leu Pro Lys Ser Gly Leu Trp Trp
 115 120 125
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 aatgaagaa actagtgaat gatgcagtgt gtagaccaga gacctctttg ggtatcaggg 860
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Trp His Thr Arg Asp Ala Met Glu Ser Asp Leu Leu Trp Thr Tyr Tyr
 35 40 45

Leu Asn Trp Cys Ser Asp Ile Phe Tyr Met Phe Ala Gly Ile Ile Ser
 50 55 60

Leu Leu Asn Tyr Leu Thr Ser Arg Ser Pro Ala Cys Asp Glu Asn Val
 65 70 75 80

Thr Val Ile Pro Thr Glu Arg Ser Arg Leu Gly Val Gly Pro Val Thr
 85 90 95

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 100 105 110

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 115 120 125

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16U 200 PCT FINAL.ST25

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gctgtgagaa gccaaggaca ccgagtcagt c atg gca cct aag gcg gca aag      172
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ggg gcc aag cca gag cca gca cca gct cca cct cca ccc ggg gcc aaa      220
Gly Ala Lys Pro Glu Pro Ala Pro Ala Pro Pro Pro Pro Gly Ala Lys
          10           15           20

ccc gag gaa gac aag aag gac ggt aag gag cca tcg gac aaa cct caa      268
Pro Glu Glu Asp Lys Lys Asp Gly Lys Glu Pro Ser Asp Lys Pro Gln
          25           30           35

aag gcg gtg cag gac cat aag gag cca tcg gac aaa cct caa aag gcg      316
Lys Ala Val Gln Asp His Lys Glu Pro Ser Asp Lys Pro Gln Lys Ala
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gtg cag ccc aag cac gaa gtg ggc acg agg agg ggg tgt cgc cgc tac      364
Val Gln Pro Lys His Glu Val Gly Thr Arg Arg Gly Cys Arg Arg Tyr
          60           65           70

cgg tgg gaa tta aaa gac agc aat aaa gag ttc tgg ctc ttg ggg cac      412
Arg Trp Glu Leu Lys Asp Ser Asn Lys Glu Phe Trp Leu Leu Gly His
          75           80           85

gct gag atc aag att cgg agt ttg ggc tgc cta ata gct gca atg ata      460
Ala Glu Ile Lys Ile Arg Ser Leu Gly Cys Leu Ile Ala Ala Met Ile
          90           95           100

ctg ttg tcc tca ctc acc gtg cac ccc atc ttg agg ctt atc atc acc      508
Leu Leu Ser Ser Leu Thr Val His Pro Ile Leu Arg Leu Ile Ile Thr
          105           110           115

atg gag ata tcc ttc ttc agc ttc ttc atc tta ctg tac agc ttt gcc      556
Met Glu Ile Ser Phe Phe Ser Phe Phe Ile Leu Leu Tyr Ser Phe Ala
          120           125           130           135

att cat aga tac ata ccc ttc atc ctg tgg ccc att tct gac ctc ttc      604
Ile His Arg Tyr Ile Pro Phe Ile Leu Trp Pro Ile Ser Asp Leu Phe
          140           145           150

aac gac ctg att gct tgt gcg ttc ctt gtg gga gcc gtg gtc ttt gct      652
Asn Asp Leu Ile Ala Cys Ala Phe Leu Val Gly Ala Val Val Phe Ala
          155           160           165

gtg aga agt cgg cga tcc atg aat ctc cac tac tta ctt gct gtg atc      700
Val Arg Ser Arg Arg Ser Met Asn Leu His Tyr Leu Leu Ala Val Ile
          170           175           180

ctt att ggt gcg gct gga gtt ttt gct ttt atc gat gtg tgt ctt caa      748
Leu Ile Gly Ala Ala Gly Val Phe Ala Phe Ile Asp Val Cys Leu Gln
          185           190           195

aga aac cac ttc aga ggc aag aag gcc aaa aag cat atg ctg gtt cct      796
-Arg Asn His Phe Arg Gly Lys Lys Ala Lys Lys His Met Leu Val Pro
          200           205           210           215

cct cca gga aag gaa aaa gga ccc cag cag ggc aag gga cca gaa ccc      844
Pro Pro Gly Lys Glu Lys Gly Pro Gln Gln Gly Lys Gly Pro Glu Pro
          220           225           230

gcc aag cca cca gaa cct ggc aag cca cca ggg cca gca aag gga aag      892
Ala Lys Pro Pro Glu Pro Gly Lys Pro Pro Gly Pro Ala Lys Gly Lys
          235           240           245

aaa tgacttgag gaggtcctg gtgtctgaaa cggcagtga ttttacagca      945
Lys

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accacctttg cttggaaaaa aatggattaa tggattctaa aagcctaaa      1054

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 35 40 45

Ser Asp Lys Pro Gln Lys Ala Val Gln Pro Lys His Glu Val Gly Thr
 50 55 60

Arg Arg Gly Cys Arg Arg Tyr Arg Trp Glu Leu Lys Asp Ser Asn Lys
 65 70 75 80

Glu Phe Trp Leu Leu Gly His Ala Glu Ile Lys Ile Arg Ser Leu Gly
 85 90 95

Cys Leu Ile Ala Ala Met Ile Leu Leu Ser Ser Leu Thr Val His Pro
 100 105 110

Ile Leu Arg Leu Ile Ile Thr Met Glu Ile Ser Phe Phe Ser Phe Phe
 115 120 125

Ile Leu Leu Tyr Ser Phe Ala Ile His Arg Tyr Ile Pro Phe Ile Leu
 130 135 140

Trp Pro Ile Ser Asp Leu Phe Asn Asp Leu Ile Ala Cys Ala Phe Leu
 145 150 155 160

Val Gly Ala Val Val Phe Ala Val Arg Ser Arg Arg Ser Met Asn Leu
 165 170 175

His Tyr Leu Leu Ala Val Ile Leu Ile Gly Ala Ala Gly Val Phe Ala
 180 185 190

Phe Ile Asp Val Cys Leu Gln Arg Asn His Phe Arg Gly Lys Lys Ala
 195 200 205

Lys Lys His Met Leu Val Pro Pro Pro Gly Lys Glu Lys Gly Pro Gln
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Gln Gly Lys Gly Pro Glu Pro Ala Lys Pro Pro Glu Pro Gly Lys Pro
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Pro Gly Pro Ala Lys Gly Lys Lys
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<222> (17)..(418)

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 Leu Leu Leu Leu Ser Asn Trp Leu Val Lys Tyr Glu His Lys Leu
 15 20 25

 acc ctc cca gag ccc cag cag gag gaa gag aaa cca aag act tct gaa 148
 Thr Leu Pro Glu Pro Gln Gln Glu Glu Glu Lys Pro Lys Thr Ser Glu
 30 35 40

 aac gac tcc aag aac agc aag gcc gtg aac aca aaa gaa gtc aat aga 196
 Asn Asp Ser Lys Asn Ser Lys Ala Val Asn Thr Lys Glu Val Asn Arg
 45 50 55 60

 acg cat gcc tgc ttt gcc ctc cag gac gag atc ctc caa cgg ctg ttg 244
 Thr His Ala Cys Phe Ala Leu Gln Asp Glu Ile Leu Gln Arg Leu Leu
 65 70 75

 ttc agt gaa atg aag atg aag gtc cta gaa aat cag atg ttc atc ata 292
 Phe Ser Glu Met Lys Met Lys Val Leu Glu Asn Gln Met Phe Ile Ile
 80 85 90

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 Trp Asn Lys Met Asn His His Gly Arg Ser Ser Arg His Arg Asn Phe
 95 100 105

 ccc atg aaa aaa cac aga atg agg agg cat gag tca att tgc ccc acc 388
 Pro Met Lys Lys His Arg Met Arg Arg His Glu Ser Ile Cys Pro Thr
 110 115 120

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<212> PRT

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 Pro Gln Gln Glu Glu Glu Lys Pro Lys Thr Ser Glu Asn Asp Ser Lys
 35 40 45

 Asn Ser Lys Ala Val Asn Thr Lys Glu Val Asn Arg Thr His Ala Cys
 50 55 60

 Phe Ala Leu Gln Asp Glu Ile Leu Gln Arg Leu Leu Phe Ser Glu Met
 65 70 75 80

 Lys Met Lys Val Leu Glu Asn Gln Met Phe Ile Ile Trp Asn Lys Met
 85 90 95

 Asn His His Gly Arg Ser Ser Arg His Arg Asn Phe Pro Met Lys Lys
 100 105 110

 His Arg Met Arg Arg His Glu Ser Ile Cys Pro Thr Leu Ser Asp Cys

16U 200 PCT FINAL-ST25
125

115

120

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 Met Asp Ser
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 Gln Gln Glu Asp Leu Arg Phe Pro Gly Met Trp Val Ser Leu Tyr Phe
 5 10 15
 gga atc ctg ggg ctg tgt tct gtg ata act gga ggg tgc att atc ttt 212
 Gly Ile Leu Gly Leu Cys Ser Val Ile Thr Gly Gly Cys Ile Ile Phe
 20 25 30 35
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 Leu His Trp Arg Lys Asn Leu Arg Arg Glu Glu His Ala Gln Gln Trp
 40 45 50
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 Val Glu Val Met Arg Ala Ala Thr Phe Thr Tyr Ser Pro Leu Leu Tyr
 55 60 65
 tgg att aac aag cga cgg cgc tac ggc atg aat gca gcc atc aac acg 356
 Trp Ile Asn Lys Arg Arg Arg Tyr Gly Met Asn Ala Ala Ile Asn Thr
 70 75 80
 ggc cct gcc cct gct gtc acc aag act gag act gag gtc cag aat cca 404
 Gly Pro Ala Pro Ala Val Thr Lys Thr Glu Thr Glu Val Gln Asn Pro
 85 90 95
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 Asp Val Leu Trp Asp Leu Asp Ile Pro Glu Gly Arg Ser His Ala Asp
 100 105 110 115
 caa gac agc aac ccc aag gcg gaa gcc cct gct ccc ctg caa cct gca 500
 Gln Asp Ser Asn Pro Lys Ala Glu Ala Pro Ala Pro Leu Gln Pro Ala
 120 125 130
 ctg cag ctg gct cca cag cag ccc cag gcc aga tcc cca ttc cca ctt 548
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 135 140 145
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 Pro Ile Phe Gln Glu Val Pro Phe Ala Pro Pro Leu Cys Asn Leu Pro
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 Pro Leu Leu Asn His Ser Val Ser Tyr Pro Leu Ala Thr Cys Pro Glu
 165 170 175
 agg aat gtt ctc ttc cat tcc ctc ctg aat ctg gcc cag gaa gac cat 692
 Arg Asn Val Leu Phe His Ser Leu Leu Asn Leu Ala Gln Glu Asp His
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 agc ttc aat gcc aag cct ttt cct tca gaa ctg tagcctctc tcaactgaagg 745
 Ser Phe Asn Ala Lys Pro Phe Pro Ser Glu Leu
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16U 200 PCT FINAL.ST25

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 35 40 45

Gln Gln Trp Val Glu Val Met Arg Ala Ala Thr Phe Thr Tyr Ser Pro
 50 55 60

Leu Leu Tyr Trp Ile Asn Lys Arg Arg Arg Tyr Gly Met Asn Ala Ala
 65 70 75 80

Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr Glu Thr Glu Val
 85 90 95

Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro Glu Gly Arg Ser
 100 105 110

His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala Pro Ala Pro Leu
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 130 135 140

Phe Pro Leu Pro Ile Phe Gln Glu Val Pro Phe Ala Pro Pro Leu Cys
 145 150 155 160

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Cys Pro Glu Arg Asn Val Leu Phe His Ser Leu Leu Asn Leu Ala Gln
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 Asp Asn Leu Leu Glu Ser Leu Ser Leu Ser Thr Val Trp Asn Trp Ile
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 Gly Leu Leu Asp Asn Leu Ala Pro Ala Val Gln Ile Ile Leu Arg Ile
 40 45 50
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 Ser Phe Leu Ile Leu Leu Gly Ile Gly Ile Tyr Ala Leu Trp Lys Arg
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 Ser Ile Gln Ser Ile Gln Lys Thr Leu Leu Phe Val Ile Thr Leu Tyr
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 Lys Leu Tyr Lys Lys Gly Ser His Ile Phe Glu Ala Leu Leu Ala Asn
 90 95 100
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 150 155 160 165
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 Ile Ile Leu Arg Ile Ser Phe Leu Ile Leu Leu Gly Ile Gly Ile Tyr
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 Ala Leu Trp Lys Arg Ser Ile Gln Ser Ile Gln Lys Thr Leu Leu Phe
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 Val Ile Thr Leu Tyr Lys Leu Tyr Lys Lys Gly Ser His Ile Phe Glu
 85 90 95

16U 200 PCT FINAL.ST25

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Met Phe Val Gly Val Ala Arg His Ser Gly Ser Gln Asp Glu
1 5 10

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Val Ser Arg Gly Val Glu Pro Leu Glu Ala Ala Arg Ala Gln Pro Ala
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Lys Asp Arg Arg Ala Lys Gly Thr Pro Lys Ser Ser Lys Pro Gly Lys
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Lys His Arg Tyr Leu Arg Leu Leu Glu Ala Leu Ile Arg Phe Gly
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Gly Phe Arg Lys Arg Lys Lys Glu Lys Ser Ser Val Ser Lys Lys Pro
65 70 75

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Gly Glu Val Asp Asp Ser Leu Glu Gln Pro Cys Gly Leu Gly Cys Leu
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Val Ser Thr Cys Cys Glu Cys Cys Asn Asn Ile Arg Cys Phe Met Ile
95 100 105 110

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Asp Val Ser Ile Gly Asp Phe Gln Lys Glu Tyr Gln Leu Lys Thr Ile
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Glu Lys Leu Ala Leu Glu Lys Ser Tyr Asp Ile Ser Ser Gly Leu Val
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195 200 205

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Gln Gly Ile Ala Gly Met Pro Leu Tyr Ile Leu Gly Ile Thr Phe Ile
240 245 250

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255 260 265 270

gaa tgt aca tca atg att gga tat gct ctg ggt tat gtg cta gga gca 985
Glu Cys Thr Ser Met Ile Gly Tyr Ala Leu Gly Tyr Val Leu Gly Ala
275 280 285

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Val Asn Asn Gly Ser Pro Glu Trp Leu Trp Thr Trp Trp Ile Asn Phe
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320 325 330

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Phe Pro Asn Asn Met Pro Gly Ser Thr Arg Ile Lys Ala Arg Lys Arg
335 340 345 350

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Thr Asn Ile Lys Asp Leu Cys Ala Ala Leu Trp Ile Leu Met Arg Asn
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385 390 395

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Ile Ile Gly Ala Ser Glu Phe Leu Pro Ile Tyr Leu Glu Asn Gln Phe
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415 420 425 430

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Pro Gly Gly Ala Leu Gly Gln Leu Leu Gly Gly Val Ile Val Ser Thr
435 440 445

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Val Ile Ser Leu Ile Leu Leu Val Phe Ile Ile Phe Val Arg Cys Asn
465 470 475

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515 520 525

1753
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Ala Cys Phe Ala Gly Cys Thr Tyr Ser Lys Ala Gln Asn Gln Lys Lys
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545 550 555

1849
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Ala Glu Gly Asp Phe Ile Asp Ala Arg Pro Gly Lys Cys Asp Ala Lys
560 565 570

1897
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575 580 585 590

1945
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595 600 605

1993
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Val Pro Asp Lys Leu Arg Ser Leu Ala Leu Gly Val Ser Tyr Val Ile
610 615 620

2041
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625 630 635

2089
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2137
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655 660 665 670

2185
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Gly Ile Cys Phe Leu Cys Lys Leu Cys Thr Ile Ile Phe Thr Thr Ile
675 680 685

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690 695 700

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705 710 715

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Leu

2394
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 Arg Tyr Leu Arg Leu Leu Pro Glu Ala Leu Ile Arg Phe Gly Gly Phe
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 Arg Lys Arg Lys Lys Ala Lys Ser Ser Val Ser Lys Lys Pro Gly Glu
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 Val Asp Asp Ser Leu Glu Gln Pro Cys Gly Leu Gly Cys Leu Val Ser
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 245 250 255
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 260 265 270
 Thr Ser Met Ile Gly Tyr Ala Leu Gly Tyr Val Leu Gly Ala Pro Leu
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Page 161

160 200 PCT FINAL.ST25
 Thr Ser Cys Ile Leu Arg Asp Val Asn Lys Cys Gly His Thr Gly Arg
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 Cys Pro Leu Gly Gln Ala Leu Trp Ala Gly Leu Ala Leu Ile Gln Val
 75 80 85

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16U 200 PCT FINAL.ST25

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 185 190 195

cac ctg gcc tat ctg atc acc tgg acc acc tgc ctg gcc tcc cac ctg 678
 His Leu Ala Tyr Leu Ile Thr Trp Thr Thr Cys Leu Ala Ser His Leu
 200 205 210

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Gly Leu Ala Gln Glu Ala Arg Gly Ser Cys Asn Trp Gln Ala His Leu
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 65 70 75 80

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 85 90 95

Leu Met Trp Ala Gly Met Trp Gly Ser Thr Lys Gly Leu Gly Leu Ala
 100 105 110

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 115 120 125

Asp Leu Phe Leu Ser Cys Leu His Gly Leu Met Leu Val Ala Leu Leu
 130 135 140

Leu Val Val Val Thr Trp Arg Val Cys Gln Lys Ser His Cys Phe Arg
 145 150 155 160

Leu Gly Arg Gln Leu Ser Lys Ala Leu Gln Val Asn Cys Val Val Arg
 165 170 175

Lys Leu Leu Val Gln Leu Arg Arg Leu Tyr Trp Trp Val Glu Thr Met
 180 185 190

160 200 PCT FINAL.ST25

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 195 200 205

Cys Leu Ala Ser His Leu Leu Gln Ala Ala Phe Glu His Thr Thr Gln
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 Met Lys Lys Ile Glu Ile
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agt ggg acg tgt ctt tcc ttt cat ctc ctt ttc ggc ttg gaa atc aga 162
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 25 30 35

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 Val Ile Leu Phe Arg Leu Leu Gly Val Ile Leu Phe Gly Arg Leu Gly
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 Asp Leu Gly Thr Cys Gln Thr Lys Pro Gly Gln Tyr Trp Lys Glu Glu
 55 60 65 70

gtc cac att caa gat gtt gga ggt ttg att tgc aga gca tgc aat ctt 354
 Val His Ile Gln Asp Val Gly Gly Leu Ile Cys Arg Ala Cys Asn Leu
 75 80 85

tca ctg ccc ttc cat gga tgt ctt tta gac ctg gga acc tgc cag gca 402
 Ser Leu Pro Phe His Gly Cys Leu Leu Asp Leu Gly Thr Cys Gln Ala
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 Glu Pro Gly Gln Tyr Cys Lys Glu Glu Val His Ile Gln Gly Gly Ile
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caa tgg tat tca gtc aaa ggc tgc aca aag aac aca tca gag tgc ttc 498
 Gln Trp Tyr Ser Val Lys Gly Cys Thr Lys Asn Thr Ser Glu Cys Phe
 120 125 130

aag agt act ctc gtc aag aga att ctg caa ctg cat gaa ctt gta act 546
 Lys Ser Thr Leu Val Lys Arg Ile Leu Gln Leu His Glu Leu Val Thr
 135 140 145 150

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 Thr His Cys Cys Asn His Ser Leu Cys Asn Phe
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160 200 PCT FINAL.ST25

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 35 40 45

Leu Phe Gly Arg Leu Gly Asp Leu Gly Thr Cys Gln Thr Lys Pro Gly
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Gln Tyr Trp Lys Glu Glu Val His Ile Gln Asp Val Gly Gly Leu Ile
 65 70 75 80

Cys Arg Ala Cys Asn Leu Ser Leu Pro Phe His Gly Cys Leu Leu Asp
 85 90 95

Leu Gly Thr Cys Gln Ala Glu Pro Gly Gln Tyr Cys Lys Glu Glu Val
 100 105 110

His Ile Gln Gly Gly Ile Gln Trp Tyr Ser Val Lys Gly Cys Thr Lys
 115 120 125

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 Gly Ala Ser Lys His Lys Leu His Tyr Arg Lys Glu Val Glu Ile Thr
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acc aca ctt cag gaa ttg tta ctc tac ttt att ttt tta ata aac cta 149

16U 200 PCT FINAL.ST25

Thr Thr Leu Gln Glu Leu Leu Leu Tyr Phe Ile Phe Leu Ile Asn Leu	
30 35 40	
tgt ata ttg act ttt ggg atg gta aac cca cat atg tat tac tta aac	197
Cys Ile Leu Thr Phe Gly Met Val Asn Pro His Met Tyr Tyr Leu Asn	
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Lys Val Met Ser Ser Leu Phe Leu Asp Thr Ser Val Pro Gly Glu Glu	
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Arg Thr Asn Phe Lys Ser Ile Arg Ser Ile Thr Asp Phe Trp Lys Phe	
75 80 85 90	
atg gaa gga ccc ctt ttg gaa ggt ctg tac tgg gat tca tgg tac aat	341
Met Glu Gly Pro Leu Leu Glu Gly Leu Tyr Trp Asp Ser Trp Tyr Asn	
95 100 105	
aac cag cag ctg tat aat tta aag aac agc agt cgc atc tac tat gaa	389
Asn Gln Gln Leu Tyr Asn Leu Lys Asn Ser Ser Arg Ile Tyr Tyr Glu	
110 115 120	
aat ata ctt cta gga gtt ccc aga gtt cgt caa cta aaa gtc cgc aac	437
Asn Ile Leu Leu Gly Val Pro Arg Val Arg Gln Leu Lys Val Arg Asn	
125 130 135	
aac aca tgc aaa gtc tat tca tct ttt cag tct ttg atg agt gaa tgt	485
Asn Thr Cys Lys Val Tyr Ser Ser Phe Gln Ser Leu Met Ser Glu Cys	
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tat ggc aaa tat act tct gca aat gaa gac ctg tct aat ttt ggc ctt	533
Tyr Gly Lys Tyr Thr Ser Ala Asn Glu Asp Leu Ser Asn Phe Gly Leu	
155 160 165 170	
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Gln Ile Asn Thr Glu Trp Arg Tyr Ser Thr Ser Asn Thr Asn Ser Pro	
175 180 185	
tgg cac tgg gga ttt ctt ggt gtt tac cga aat ggg gga tac att ttc	629
Trp His Trp Gly Phe Leu Gly Val Tyr Arg Asn Gly Gly Tyr Ile Phe	
190 195 200	
act tta tca aaa tcg aaa tct gaa acc aaa aac aag ttc att gac ctt	677
Thr Leu Ser Lys Ser Lys Ser Glu Thr Lys Asn Lys Phe Ile Asp Leu	
205 210 215	
cga ctg aac agc tgg atc aca aga ggg act aga gtt att ttt att gat	725
Arg Leu Asn Ser Trp Ile Thr Arg Gly Thr Arg Val Ile Phe Ile Asp	
220 225 230	
ttt tcc tta tat aat gct aat gta aat cta ttt tgt att atc aga ttg	773
Phe Ser Leu Tyr Asn Ala Asn Val Asn Leu Phe Cys Ile Ile Arg Leu	
235 240 245 250	
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Val Ala Glu Phe Pro Ala Thr Gly Gly Ile Leu Thr Ser Trp Gln Phe	
255 260 265	
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-Tyr Ser Val Lys Leu Leu Arg Tyr Val Ser Tyr Tyr Asp Tyr Phe Ile	
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Ala Ser Cys Glu Ile Thr Phe Cys Ile Phe Leu Phe Val Phe Thr Thr	
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Gln Glu Val Lys Lys Ile Lys Glu Phe Lys Ser Ala Tyr Phe Lys Ser	
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Ile Trp Asn Trp Leu Glu Leu Leu Leu Leu Cys Phe Val Ala	
315 320 325 330	
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Val Ser Phe Asn Thr Tyr Tyr Asn Val Gln Ile Phe Leu Leu Leu Gly	
335 340 345	

160 200 PCT FINAL.ST25

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Gln Leu Leu Lys Ser Thr Glu Lys Tyr Ser Asp Phe Tyr Phe Leu Ala
350 355 360

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Cys Trp His Ile Tyr Tyr Asn Asn Ile Ile Ala Ile Thr Ile Phe Phe
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Ala Trp Ile Lys Ile Phe Lys Phe Ile Ser Phe Asn Lys Thr Met Ser
380 385 390

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Gln Leu Ser Ser Thr Leu Ser Arg Cys Val Lys Asp Ile Val Gly Phe
395 400 405 410

gcc atc atg ttt ttt ata ata ttc ttt gct tat gcc cag tta gga ttt 1301
Ala Ile Met Phe Phe Ile Ile Phe Phe Ala Tyr Ala Gln Leu Gly Phe
415 420 425

ctt gtt ttt gga tca caa gtt gat gac ttt tcc act ttt cag aat tcc 1349
Leu Val Phe Gly Ser Gln Val Asp Asp Phe Ser Thr Phe Gln Asn Ser
430 435 440

ata ttt gca caa ttt cga att gtt ctt gga gat ttt aat ttt gct ggt 1397
Ile Phe Ala Gln Phe Arg Ile Val Leu Gly Asp Phe Asn Phe Ala Gly
445 450 455

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460 465 470

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475 480 485 490

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Asn Asp Thr Tyr Ser Glu Val Lys Ala Asp Tyr Ser Ile Gly Arg Arg
495 500 505

cca gat ttt gaa ctt ggc aaa atg att aaa cag agt tac aaa aat gtt 1589
Pro Asp Phe Glu Leu Gly Lys Met Ile Lys Gln Ser Tyr Lys Asn Val
510 515 520

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Leu Glu Lys Phe Arg Leu Lys Lys Ala Gln Lys Asp Glu Asp Lys Lys
525 530 535

acc aaa ggc agc gga gat ttg gct gaa caa gcc aga aga gaa ggc ttt 1685
Thr Lys Gly Ser Gly Asp Leu Ala Glu Gln Ala Arg Arg Glu Gly Phe
540 545 550

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Asp Glu Asn Glu Ile Gln Asn Ala Glu Gln Met Lys Lys Trp Lys Glu
555 560 565 570

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Arg Leu Glu Lys Lys Tyr Tyr Ser Met Glu Ile Gln Asp Asp Tyr Gln
575 580 585

cct gtc act caa gaa gaa ttt cga gat ggc acc aca acc aag tac aaa 1829
Pro Val Thr Gln Glu Glu Phe Arg Asp Gly Thr Thr Thr Lys Tyr Lys
590 595 600

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Met Arg Phe Ser Leu Ser Ala
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16U 200 PCT FINAL.ST25

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<400> 253

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 35 40 45

Met Val Asn Pro His Met Tyr Tyr Leu Asn Lys Val Met Ser Ser Leu
 50 55 60

Phe Leu Asp Thr Ser Val Pro Gly Glu Glu Arg Thr Asn Phe Lys Ser
 65 70 75 80

Ile Arg Ser Ile Thr Asp Phe Trp Lys Phe Met Glu Gly Pro Leu Leu
 85 90 95

Glu Gly Leu Tyr Trp Asp Ser Trp Tyr Asn Asn Gln Gln Leu Tyr Asn
 100 105 110

Leu Lys Asn Ser Ser Arg Ile Tyr Tyr Glu Asn Ile Leu Leu Gly Val
 115 120 125

Pro Arg Val Arg Gln Leu Lys Val Arg Asn Asn Thr Cys Lys Val Tyr
 130 135 140

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Ala Asn Glu Asp Leu Ser Asn Phe Gly Leu Gln Ile Asn Thr Glu Trp
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Arg Tyr Ser Thr Ser Asn Thr Asn Ser Pro Trp His Trp Gly Phe Leu
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Gly Val Tyr Arg Asn Gly Gly Tyr Ile Phe Thr Leu Ser Lys Ser Lys
 195 200 205

Ser Glu Thr Lys Asn Lys Phe Ile Asp Leu Arg Leu Asn Ser Trp Ile
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Thr Arg Gly Thr Arg Val Ile Phe Ile Asp Phe Ser Leu Tyr Asn Ala
 225 230 235 240

Asn Val Asn Leu Phe Cys Ile Ile Arg Leu Val Ala Glu Phe Pro Ala
 245 250 255

Thr Gly Gly Ile Leu Thr Ser Trp Gln Phe Tyr Ser Val Lys Leu Leu
 260 265 270

Arg Tyr Val Ser Tyr Tyr Asp Tyr Phe Ile Ala Ser Cys Glu Ile Thr
 275 280 285

16U 200 PCT FINAL.ST25

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 305 310 315 320
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 325 330 335
 Tyr Asn Val Gln Ile Phe Leu Leu Leu Gly Gln Leu Leu Lys Ser Thr
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 Glu Lys Tyr Ser Asp Phe Tyr Phe Leu Ala Cys Trp His Ile Tyr Tyr
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 Asn Asn Ile Ile Ala Ile Thr Ile Phe Phe Ala Trp Ile Lys Ile Phe
 370 375 380
 Lys Phe Ile Ser Phe Asn Lys Thr Met Ser Gln Leu Ser Ser Thr Leu
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 Ser Arg Cys Val Lys Asp Ile Val Gly Phe Ala Ile Met Phe Phe Ile
 405 410 415
 Ile Phe Phe Ala Tyr Ala Gln Leu Gly Phe Leu Val Phe Gly Ser Gln
 420 425 430
 Val Asp Asp Phe Ser Thr Phe Gln Asn Ser Ile Phe Ala Gln Phe Arg
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 465 470 475 480
 Val Leu Leu Asn Met Phe Leu Ala Ile Ile Asn Asp Thr Tyr Ser Glu
 485 490 495
 Val Lys Ala Asp Tyr Ser Ile Gly Arg Arg Pro Asp Phe Glu Leu Gly
 500 505 510
 Lys Met Ile Lys Gln Ser Tyr Lys Asn Val Leu Glu Lys Phe Arg Leu
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 Lys Lys Ala Gln Lys Asp Glu Asp Lys Lys Thr Lys Gly Ser Gly Asp
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 Asn Ala Glu Gln Met Lys Lys Trp Lys Glu Arg Leu Glu Lys Lys Tyr
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16U 200. PCT FINAL.ST25
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 Ala Ile Arg Ser Arg Leu Ile Asp Thr Phe Ser Leu Ile Glu His Leu
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 caa ggc ttg agc caa gct gtg ccg cgg cac act atc agg gag tta ctt 144
 Gln Gly Leu Ser Gln Ala Val Pro Arg His Thr Ile Arg Glu Leu Leu
 35 40 45
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 Asp Pro Ser Arg Gln Lys Lys Leu Val Leu Gly Asp Gln His Gln Leu
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 Val Arg Phe Ser Ile Lys Pro Gln Arg Ile Glu Gln Ile Ser His Ala
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 Gln Arg Leu Leu Ser Arg Leu His Val Arg Cys Ser Gln Arg Pro Pro
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 Thr Leu Glu Val Ala Ala Trp Phe Ile Leu Leu Ile Phe Ile Leu Glu
 145 150 155 160
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 180 185 190
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 195 200 205
 ctg agg atc tgc cgg gtg ctg agg tct ctc aaa ctc ctt gca caa ttc 672
 Leu Arg Ile Cys Arg Val Leu Arg Ser Leu Lys Leu Leu Ala Gln Phe
 210 215 220
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 Arg Gln Ile Gln Ile Ile Ile Leu Val Leu Val Arg Ala Leu Lys Ser
 225 230 235 240
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16U 200 PCT FINAL.ST25
Met Thr Phe Leu Leu Met Leu Leu Leu Ile Phe Phe Tyr Ile Phe Ala
245 250 255

gtg act ggt gtc tac gtc ttc tca gag tac acc cgt tca cct cgt cag 816
Val Thr Gly Val Tyr Val Phe Ser Glu Tyr Thr Arg Ser Pro Arg Gln
260 265 270

gac ctg gag tac cat gtg ttc ttc tgc gac ctc ccg aat tcc ctg gta 864
Asp Leu Glu Tyr His Val Phe Phe Ser Asp Leu Pro Asn Ser Leu Val
275 280 285

aca gtg ttc att ctc ttc acc ttg gat cat tgg tat gca ctg ctt cag 912
Thr Val Phe Ile Leu Phe Thr Leu Asp His Trp Tyr Ala Leu Leu Gln
290 295 300

gac gtc tgg aag gtg cct gaa gtc agt cgc atc ttc agc agc atc tat 960
Asp Val Trp Lys Val Pro Glu Val Ser Arg Ile Phe Ser Ser Ile Tyr
305 310 315 320

ttc atc ctt tgg ttg ttg ctt ggc tcc att atc ttt cga agt atc ata 1008
Phe Ile Leu Trp Leu Leu Leu Gly Ser Ile Ile Phe Arg Ser Ile Ile
325 330 335

gta gcc atg atg gtt act aac ttt cag aat atc agg aaa gag ctg aat 1056
Val Ala Met Met Val Thr Asn Phe Gln Asn Ile Arg Lys Glu Leu Asn
340 345 350

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Glu Glu Met Ala Arg Arg Glu Val Gln Leu Lys Ala Asp Met Phe Lys
355 360 365

cgg cag atc atc cag agg aga aaa aac atg tca cat gaa gca ctg acg 1152
Arg Gln Ile Ile Gln Arg Arg Lys Asn Met Ser His Glu Ala Leu Thr
370 375 380

tca agc cat agc aaa ata gag gac aga gga gct agt caa caa agg gaa 1200
Ser Ser His Ser Lys Ile Glu Asp Arg Gly Ala Ser Gln Gln Arg Glu
385 390 395 400

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405 410 415

act gaa gag gat tta ata aca tct gca tca aaa aca gaa gag acc ttg 1296
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420 425 430

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Ser Lys Lys Arg Glu Tyr Gln Ser Ser Ser Cys Val Ser Ser Thr Ser
435 440 445

tct tcc tat tct tcc tct tct gaa tcc aga ttt tct gaa tct att ggt 1392
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450 455 460

cgt ttg gac tgg gag act ctt gtg cac gaa aat ctg ccc ggg cta atg 1440
Arg Leu Asp Trp Glu Thr Leu Val His Glu Asn Leu Pro Gly Leu Met
465 470 475 480

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Glu Met Asp Gln Asp Asp Arg Val Trp Pro Arg Asp Ser Leu Phe Arg
485 490 495

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Tyr Phe Glu Leu Leu Glu Lys Leu Gln Tyr Asn Leu Glu Glu Arg Lys
500 505 510

aag tta caa gag ttt gca gtg cag gca ctg atg aac ttg gaa gac aag 1584
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16U 200 PCT FINAL.ST25

<400> 255

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 35 40 45

Asp Pro Ser Arg Gln Lys Lys Leu Val Leu Gly Asp Gln His Gln Leu
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Val Arg Phe Ser Ile Lys Pro Gln Arg Ile Glu Gln Ile Ser His Ala
 65 70 75 80

Gln Arg Leu Leu Ser Arg Leu His Val Arg Cys Ser Gln Arg Pro Pro
 85 90 95

Leu Ser Leu Trp Ala Gly Trp Val Leu Glu Cys Pro Leu Phe Lys Asn
 100 105 110

Phe Ile Ile Phe Leu Val Phe Leu Asn Thr Ile Ile Leu Met Val Glu
 115 120 125

Ile Glu Leu Leu Glu Ser Thr Asn Thr Lys Leu Trp Pro Leu Lys Leu
 130 135 140

Thr Leu Glu Val Ala Ala Trp Phe Ile Leu Leu Ile Phe Ile Leu Glu
 145 150 155 160

Ile Leu Leu Lys Trp Leu Ser Asn Phe Ser Val Phe Trp Lys Ser Ala
 165 170 175

Trp Asn Val Phe Asp Phe Val Val Thr Met Leu Ser Leu Leu Pro Glu
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Val Val Val Leu Val Gly Val Thr Gly Gln Ser Val Trp Leu Gln Leu
 195 200 205

Leu Arg Ile Cys Arg Val Leu Arg Ser Leu Lys Leu Leu Ala Gln Phe
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Arg Gln Ile Gln Ile Ile Ile Leu Val Leu Val Arg Ala Leu Lys Ser
 225 230 235 240

Met Thr Phe Leu Leu Met Leu Leu Leu Ile Phe Phe Tyr Ile Phe Ala
 245 250 255

Val Thr Gly Val Tyr Val Phe Ser Glu Tyr Thr Arg Ser Pro Arg Gln
 260 265 270

Asp Leu Glu Tyr His Val Phe Phe Ser Asp Leu Pro Asn Ser Leu Val
 275 280 285

Thr Val Phe Ile Leu Phe Thr Leu Asp His Trp Tyr Ala Leu Leu Gln
 290 295 300

Asp Val Trp Lys Val Pro Glu Val Ser Arg Ile Phe Ser Ser Ile Tyr

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Val	Ala	Met	Met	Val	Thr	Asn	Phe	Gln	Asn	Ile	Arg	Lys	Glu	Leu	Asn				
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Ser	Lys	Lys	Arg	Glu	Tyr	Gln	Ser	Ser	Ser	Cys	Val	Ser	Ser	Thr	Ser				
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160 200 PCT FINAL.ST25

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